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(54) Title: LIPID PHOSPHATE PHOSPHATASES AND USES THEREOF FOR TREATING NEURONAL DISEASES

(57) Abstract: Lipid phosphate phosphatase proteins, genes coding for them, vectors and cells comprising them, antibodies directed against them, methods of identifying compounds binding to them and functional interactors as well as to the use of proteins, genes, vectors, cells, interacting compounds and functional interactors for treating neuronal diseases and/or injuries.

Lipid phosphate phosphatases and uses thereof for treating neuronal diseases

The present invention relates to lipid phosphate phosphatase proteins, genes coding for them, vectors and cells comprising them, antibodies directed against them, methods of identifying compounds binding to them and functional interactors as well as to the use of proteins, genes, vectors, cells, interacting compounds and functional interactors for treating neuronal diseases and/or injuries.

Axons in the central nervous system (CNS) elongate through the extracellular space over long distances (N. Tessier-Lavigne and C. S. Goodman (1996) Science 274:1123-1133). This occurs during development (C. S. Goodman (1996) Annu. Rev. Neurosci.19:341-377 and H. Super and E. Soriano (1994) J. Comp. Neurol. 344:101-120) and during axonal sprouting in response to partial deafferentation (C. Cotman et al. (1977) J. Neurocytol. 6:455-464 and M. Frotscher et al. (1997) Trends Neurosci. 20:218-223). The extracellular space, however, is an outgrowth repellent environment that allows axonal elongation only under specific molecular conditions (E. Stein and N. Tessier-Lavigne (2001) Science 291:1928-1938). Molecules involved in axonal outgrowth, such as semaphorins, netrins, or ephrins (S. A. Colamarino and M. Tessier-Lavigne (1995) Cell 81:621-629, H Kobayashi et al. (1997) J. Neurosci. 17:8339-8352, E. Stein et al. (1999) J. Neurosci. 19:8585-8893 and A. Steup et al. (2000) Mol. Cell Neurosci. 15:141-155) are able to transduce outgrowth promoting as well as inhibiting signals to elongating axons via specific receptors.

In the hippocampus, afferent connections from the entorhinal cortex enter in a layer-specific manner during development (T. Skutella and R. Nitsch (2001) Trends Neurosci. 24:107-113). This specific axonal navigation depends on molecular cues expressed along the pathway and in the target region (T. Skutella and R. Nitsch, *supra*). Transection of entorhinal axons in the adult leads to a specific deafferentation in the hippocampus with subsequent regenerative axon sprouting by remaining afferents into the denervated zones (C. Cotman et al, *supra* and D.A Matthews et al. (1976) Brain Res. 115:23-41). It has been shown that signaling via bioactive lipid phosphates such as phosphatidate (PA), lysophosphatidate (1- or 2-oleoyl-lysophosphatidic acid; LPA) or sphingosine-1-phosphate (S-1-P) are involved in cell migration, mitogenesis and neurite retraction (K. Jalink et al. (1994)

Biochim. Biophys. Acta 1198:185-196, W. H. Moolenaar (1995) Curr. Opin. Cell Biol. 7:203-210 and N. Zhang et al. (1997) Nature 385:64-67) and in particular it has been shown that signaling via extracellular LPA plays an important role in CNS development and that postmitotic neurons are at least one endogenous source for LPA in the nervous system (N. Fukushima et al. (2000) Dev. Biol. 228:6-18). LPA has properties of an extracellular neurite repellent factor (K. Jalink (1994) *supra* and K. Jalink et al. (1993) Cell Growth Differ. 4:247-255). It is present in the extracellular space of the nervous system (Fukushima et al. (2000) *supra* and J. Bothmer et al. (1992) Neurochem. Int. 21:223-228) and mediates diverse cellular responses through the activation of multiple signal transduction pathways (W. H. Moolenaar (1995) *supra*). One major structural effect of LPA on neurons is rapid neurite retraction with subsequent cell rounding. Therefore, LPA and similar bioactive lipid phosphatases inhibit a regrowth of axons following neuronal lesion. Therefore, it is a problem known in the art, that after neuronal damage due to, for example, neuronal disease or trauma a regrowth of axons does not occur.

Within the context of the present invention it has been found that the expression of a family of genes called plasticity-related genes (PRGs) overcomes the repellent effect of bioactive lipid phosphates, in particular of LPA and, thus, allows the regrowth of axons in spite of the presence of bioactive lipid phosphates. Therefore, the present invention is directed at an isolated protein comprising the same or substantially the same amino acid sequence selected from the group consisting of human PRG-1, human PRG-2, human PRG-3, human PRG-4, mouse PRG-1, mouse PRG-2, mouse PRG-3, mouse PRG-4, rat PRG-1, rat PRG-2, rat PRG-3, and rat PRG-4 (depicted in SEQ ID NOs: 1 to 12), respectively, or a splice variant or a salt thereof. A protein having substantially the same amino acid sequence comprises proteins with at least about 95%, preferably at least about 96%, more preferably at least about 97%, more preferably with at least about 98% and most preferably with at least about 99% amino acid sequence identity. The amino acid exchanges are preferably so called conservative changes meaning substitutions of, for example, a polar amino acid residue by another polar amino acid residue, of a acidic amino acid residue by another acidic amino acid residue or of a basic amino acid residue by another basic amino acid residue.

Proteins having substantially the same amino acid sequence within the meaning of this invention exhibit in a preferred embodiment lipid phosphate phosphatase activity The lipid

phosphate phosphatase activity of a given protein with substantially the same amino acid can be tested, for example, by the ectophosphatase assay described in example 11 below. The proteins employed in the assay can either be purified from cells or can be recombinantly expressed and purified by methods well known in the art.

In one embodiment of the present invention the protein comprises at least one fragment of the human PRG-1, PRG-2, PRG-3, and PRG-4 or mouse PRG-1, PRG-2, PRG-3 and PRG-4 or rat PRG-1, PRG-2, PRG-3 and PRG-4. A fragment within the meaning of the present invention refers to one of the proteins according to SEQ ID NOs: 1 to 12 bearing at least one N-terminal, C-terminal and/or internal deletion. The resulting fragment has a length of at least about 50, preferably of at least about 100, more preferably of at least about 150, more preferably of at least about 200, more preferably of at least about 250, more preferably of at least about 300 and in case of human PRG-1 and PRG-2 or mouse PRG-1 and PRG-2 or rat PRG-1 and rat PRG-2, more preferably of at least about 350 and most preferably of at least about 400 amino acids.

Preferably, the fragment is an N-terminal fragment which comprises 330 amino acids or less as outlined above, which are highly conserved between, for example, PRG-1 and members of the family of LPP membrane-associated phosphatic acid phosphatase ectoenzymes, which have six membrane spanning domains with their active site located on the external surface of the plasma membrane. This domain comprises preferably the catalytic region. For example, human PRG-1 carries a catalytic histidine at position 252, which is involved in the phosphatase activity of human PRG-1. Similarly human, mouse and rat PRG-3 comprises a domain highly homologous to human PRG-1, which in rat PRG-3 spans amino acids 210 to 212 and includes a histidine residue at amino acid 209. Therefore, in a preferred embodiment any N-terminal fragment of the proteins of the present invention comprises the catalytic site, preferably including the conserved His-residue. The fragment itself has preferably an amino acid sequence identity with hPRG-1, hPRG-2, hPRG-3, hPRG-4, mPRG-1, mPRG-2, mPRG-3, mPRG-4, rPRG-1, rPRG-2, rPRG-3, and rPRG-4, respectively, of at least about 95%, preferably of at least about 96%, more preferably of at least about 97%, more preferably of at least about 98%, more preferably of at least about 99% and most preferably of 100%.

The C-terminal cytoplasmatic part of the PRG proteins is potentially involved in regulation of lipid phosphate phosphatase activity and/or signaling and, thus, a further preferred fragment comprises a C-terminal fragment, which comprises about 413 amino acids or less as outlined above and which comprises regions required for above activity of the PRG proteins. The fragment itself has preferably an amino acid sequence identity with hPRG-1, hPRG-2, hPRG-3, hPRG-4, mPRG-1, mPRG-2, mPRG-3, mPRG-4, rPRG-1, rPRG-2, rPRG-3, and rPRG-4, respectively, of at least about 95%, preferably of at least about 96%, more preferably of at least about 97%, more preferably of at least about 98%, more preferably of at least about 99% and most preferably of 100%.

In a further aspect the present invention is directed at a nucleic acid, which comprises at least one nucleic acid encoding one of the proteins of the present invention. Preferably the nucleic acid consists of DNA or RNA, wherein the DNA preferentially is either single or double stranded. Also comprised are DNA's, which hybridize to one of the aforementioned DNA's preferably under stringent conditions like, for example, hybridization at 60°C in 2.5 x SSC buffer and several washes at 37°C at a lower buffer concentration like, for example, 0.5 x SSC buffer and which encode proteins exhibiting lipid phosphate phosphatase activity and/or association with plasma membranes. Additional reagents required for carrying out stringent Northern or Southern blots like, for example, single stranded salmon sperm DNA are well known in the art. Also comprised are nucleic acid sequences, which are related to the nucleic acids according to SEQ ID No. 13-24 and/or the hybridizing nucleic acids as outlined above by the degeneration of the genetic code.

In a preferred embodiment of the nucleic acid of the present invention the nucleic acid comprises a nucleic acid selected from the group consisting of the human PRG-1 gene, the human PRG-2 gene, the human PRG-3, the human PRG-4, the mouse PRG-1 gene, the mouse PRG-2 gene, the mouse PRG-3, the mouse PRG-4, the rat PRG-1, the rat PRG-2, the rat PRG-3, and the rat PRG-4 gene (see SEQ ID NOs: 13 to 24).

In a further embodiment the nucleic acid of the present invention further comprises at least one promoter, enhancer, intron and/or polyA-sequence. Preferred promoters or enhancers posses tissue specificity, in particular neuronal specificity and more particular a specificity for growing neurons. Examples of such promoters and/or enhancers are the neuron specific enolase promoter (Erickson, R.P. and Bernard, O. (2002) J. Neuro Science Res 68:738-44),

the peripherin promoter (Weinstein, D.E. et al. (1999) Brain Res. Dev. Brain Res. 116:29-39), the synapsin promoter (Flood, D.G. et al. (1999) Am. J. Pathol. 155:663-72) and the Thy 1 promoter (Kahle, P. J. et al. (2001) Am. J. Pathol. 159:2215-25).

In some instances it might be desirable to interfere with, for example, the transcription or translation of the nucleic acids of the present invention and, therefore, the present invention is also directed at a nucleic acid, which is complementary to the nucleic acid of the present invention and, thus, is capable of inhibiting, for example, transcription or translation. A preferred embodiment of such a complementary nucleic acid is a so called anti-sense oligonucleotide (R. Q. Zheng and D. M. Kemeny (1995) Clin. Exp. Immunol. 100:380-2, W. Nellen and C. Lichtenstein (1993) Trends. Biochem. Sci. 18:419-423 and C. A. Stein (1992) Leukemia 6:967-74), ribozymes (M. Amarzguioui and H. Prydz (1998) Cell. Mol. Life Sci. 54:1175-1202, N. K. Vaish et al (1998) Nucleic Acids Res. 96:5237-5242, Persidis (1997) Nat. Biotechnol. 15:921-922 and L. A. Couture and D. T. Stinchcomb (1996) Trends Genet. 12:510-515) and/or so called small interfering RNA-molecules (siRNAs) (S. M. Elbashir et al. (2001) Nature 411:494-498). Anti-sense oligonucleotides are able to decrease the stability of the above described nucleic acids and/or can inhibit the translation. Similarly the use of siRNA-oligonucleotides can also lead to a reduction in the amount of the translated polypeptides. Anti-sense oligonucleotides have in a preferred embodiment a length of at least 20, preferable of at least about 30, more preferably of at least about 40 and most preferably a length of at least about 50 nucleic acids.

Oligonucleotides are generally rapidly degraded by endo- or exonucleases, which are present in the cell, in particular by DNases und RNases and, therefore, it is advantageous to modify the nucleic acids which are used, for example, in anti-sense strategies, as ribozymes or siRNAs to stabilize them against degradation and thereby prolong the time over which an effective amount of the nucleic acid is maintained within the cell (L. Beigelmann et al. (1995) Nucleic acids Res. 23:3989-94, WO 95/11910, WO 98/37340 and WO 97/29116). Typically such stabilization can be obtained by the introduction of one or more internucleotide phosphate groups and/or by the introduction of one or more non-phosphor-internucleotides.

Suitable modified internucleotides are summarized in, for example, Uhlmann and Peimann (1990) Can. Rev. 90:544. Modified internucleotide phosphate residues and/or non-

phosphate bridges which can be used in a nucleic acid of the invention comprise, for example, methylphosphonate, phosphorthioate, phosphoramidate, phosphordithionate, phosphate ester, non-phosphor internucleotide analogues, which can be used in nucleic acids of the invention include, for example, siloxane bridges, carbonate bridges, carboxymethylester, acetamid bridges and/or thioether bridges.

A further aspect of the present invention is directed at a vector comprising a protein according to the present invention and/or a nucleic acid according to the present invention. A vector within the meaning of the present invention is a protein or a nucleic acid or a mixture thereof which is capable of being introduced or of introducing the proteins and/or nucleic acid comprised into a cell. It is preferred that the proteins encoded by the introduced nucleic acid are expressed within the cell upon introduction of the vector.

In a preferred embodiment the vector of the present invention comprises plasmids, phagemids, phages, cosmids, artificial mammalian chromosomes, knock-out or knock-in constructs, viruses, in particular adenovirus, vaccinia virus, lentivirus (Chang, L.J. and Gay, E.E. (20001) Curr. Gene Therap. 1:237-251), Herpes simplex virus (HSV-1, Carlezon, W.A. et al. (2000) Crit. Rev. Neurobiol.), baculovirus, retrovirus, adeno-associated-virus (AAV, Carter, P.J. and Samulski, R.J. (2000) J. Mol. Med. 6:17-27), rhinovirus, human immune deficiency virus (HIV), filovirus and engineered versions thereof (see, for example, Cobinger G. P. et al (2001) Nat. Biotechnol. 19:225-30), virosomes, "naked" DNA liposomes, and nucleic acid coated particles, in particular gold spheres. Particularly preferred are viral vectors like adenoviral vectors or retroviral vectors (Lindemann et al. (1997) Mol. Med. 3:466-76 and Springer et al. (1998) Mol. Cell. 2:549-58). Liposomes are usually small unilamellar or multilamellar vesicles made of neutral cationic and/or anionic lipids, for example, by ultrasound treatment of liposomal suspensions. The DNA can, for example, be ionically bound to the surface of the liposomes or internally enclosed in the liposome. Suitable lipid mixtures are known in the art and comprise, for example, cholesterol, phospholipide like, for example, phosphatidylcholin (PC), phosphatidylserin (PS) and the like, DOTMA (1, 2-Dioleyloxpropyl-3-trimethylammoniumbromid) and DPOE (Dioleoylphosphatidylethanolamin) which both have been used on a variety of cell lines.

Nucleic acid coated particles are another means for the introduction of nucleic acids into cells using so called "gene guns", which allow the mechanical introduction of particles into

the cells. Preferably the particles itself are inert, and therefore, are in a preferred embodiment made out of gold spheres.

In a further aspect the present invention is directed at an isolated cell comprising a protein of the present invention, a nucleic acid of the present invention and/or a vector of the present invention. Cells of the present invention can be prokaryotic or eukaryotic cells and in a preferred embodiment the cells of the present invention are stem cells, in particular non-human embryonic stem cells, embryonic stem cell lines, foetal stem cells, adult stem cells, neuronal precursor cells or neuronal cells in particular axons (Hsich, G. et al. (2002) Hum. Gene Therap., 13:579-604 and Martinez-Serrano, A. et al. (2001) Curr. Gene Therap. 1:279-299). The cells preferably comprise the nucleic acids extrachromosomally or interchromosomally.

A further aspect of the present invention is a transgenic non-human animal generated from a cell or cells of the present invention. The animal can be a mosaic animal, which means that only part of the cells making up the body comprise cells of the present invention or the animal can be a transgenic animal which means that all cells of the animal are derived from a cell of the present invention. Mosaic or transgenic animals can be either homo- or heterozygous with respect to the nucleic acid of the present invention contained within the cell of the present invention. In a preferred embodiment the transgenic animals are either homo- or heterozygous knock-out or knock-in animals with respect to the genes which code for the proteins of the present invention.

In a further aspect the present invention is directed at an antibody directed against a protein of the present invention. The term "antibody" comprises monoclonal and polyclonal antibodies and binding fragments thereof, in particular Fc-fragments as well as so called "single-chain-antibodies" (Bird R. E. et al (1988) Science 242:423-6) and diabodies (Holliger P. et al (1993) Proc. Natl. Acad. Sci. U.S.A. 90:6444-8).

In a further aspect the present invention is directed at a method of producing a protein of the present invention or a nucleic acid of the present invention and comprises the steps of: a) cultivating a cell of the present invention and b) isolating the protein and/or the nucleic acid. If the method is used primarily to isolate nucleic acids then in an preferred embodiment the cells, which are used are prokaryotic cells, in particular *E. coli*. cells If the

method is used primarily for the isolation of proteins of the invention than the cells can be either of prokaryotic or eukaryotic origin. Someone of skill in the art is aware of a variety of different cell types suitable for the production of proteins like, for example, *E. coli*, Sf9, Hi5, *P. pastoris*, COS and HeLa. Eukaryotic cells are preferably chosen, if it is desired that the proteins produced by the cells exhibit an essentially natural pattern of glycosylation and prokaryotic cells are chosen, if, for example, glycosylation or other modifications, which are normally introduced into proteins only in eukaryotic cells, are not desired or not needed.

In a further aspect the present invention is directed at a method of isolating compounds interacting with a protein of the present invention comprising the steps of: a) contacting one or more of the proteins of the present invention, preferably one, with at least one potentially interacting compound, and b) measuring binding of said compound to said protein. This method is suitable for the determination of compounds that can interact with the proteins of the present invention and to identify, for example, inhibitors, activators, competitors or modulators of proteins of the present invention, in particular inhibitors, activators, competitors or modulators of the enzymatic activity of the proteins of the present invention.

The potentially binding substance, whose binding to the protein of the present invention is to be measured, can be any chemical substance or any mixture thereof. For example, it can be a substance of a peptide library, a combinatory library, a cell extract, in particular a plant cell extract, a "small molecular drug", a protein and/or a protein fragment.

The term "contacting" in the present invention means any interaction between the potentially binding substance(s) with the proteins of the invention, whereby any of the two components can be independently of each other in a liquid phase, for example in solution, or in suspension or can be bound to a solid phase, for example, in the form of an essentially planar surface or in the form of particles, pearls or the like. In a preferred embodiment a multitude of different potentially binding substances are immobilized on a solid surface like, for example, on a compound library chip and the protein of the present invention is subsequently contacted with such a chip.

The proteins of the present invention employed in a method of the present invention can be full length proteins or a fragments with N/C-terminal and/or internal deletions. Preferably the fragments are either N-terminal fragments comprising the enzymatic region of the protein or C-terminal fragments comprising the cytoplasmic region, depending on whether potentially interacting compounds are sought that specifically interact with the N- or C-terminal fragment

Measuring of binding of the compound to the protein can be carried out either by measuring a marker that can be attached either to the protein or to the potentially interacting compound. Suitable markers are known to someone of skill in the art and comprise, for example, fluorescence or radioactive markers. The binding of the two components can, however, also be measured by the change of an electrochemical parameter of the binding compound or of the protein, e.g. a change of the redox properties of either the protein or the binding compound, upon binding. Suitable methods of detecting such changes comprise, for example, potentiometric methods. Further methods for detecting and/or measuring the binding of the two components to each other are known in the art and can without limitation also be used to measure the binding of the potential interacting compound to the protein or protein fragments of the present invention. The effect of the binding of the compound or the activity of the protein can also be measured indirectly, for example, by assaying the phosphatase activity of the protein after binding.

As a further step after measuring the binding of a potentially interacting compound and after having measured at least two different potentially interacting compounds at least one compound can be selected, for example, on grounds of the measured binding activity or on grounds of the detected increase or decrease of protein activity, in particular lipid phosphate phosphatase activity upon binding. The phosphatase activity can be measured, for example, as described in example 11.

The thus selected binding compound is than in a preferred embodiment modified in a further step. Modification can be effected by a variety of methods known in the art, which include without limitation the introduction of novel side chains or the exchange of functional groups like, for example, introduction of halogens, in particular F, Cl or Br, the introduction of lower alkyl groups, preferably having one to five carbon atoms like, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or iso-

pentyl groups, lower alkenyl groups, preferably having two to five carbon atoms, lower alkinyl groups, preferably having two to five carbon atoms or through the introduction of, for example, a group selected from the group consisting of NH_2, NO_2, OH, SH, NH, CN, aryl, heteroaryl, COH or COOH group.

The thus modified binding substances are than individually tested with the method of the present invention, i.e. they are contacted with the protein and subsequently binding of the modified compounds to the protein is measured. In this step both the binding per se can be measured and/or the effect of the function of the protein like, e.g. the enzymatic activity of the protein can be measured. If needed the steps of selecting the binding compound, modifying the binding compound, contacting the binding compound with a protein of the invention and measuring the binding of the modified compounds to the protein can be repeated a third or any given number of times as required. The above described method is also termed "directed evolution" since it involves a multitude of steps including modification and selection, whereby binding compounds are selected in an "evolutionary" process optimizing its capabilities with respect to a particular property, e.g. its binding activity, its ability to activate, inhibit or modulate the activity, in particular the phosphatase activity of the proteins of the present invention.

A further aspect of the present invention is a method of isolating compounds functionally interacting with the activity of the proteins of the present invention comprising the steps of: a) contacting a neuronal cell that comprises a wt nucleic acid coding for a protein selected from the group consisting of SEQ ID NOs: 1 to 12, a splice variant thereof, or a fragment thereof with a potential functional interactor, b) contacting the cell with a bioactive lipid phosphate, and c) measuring neurite movement or phosphatase activity.

The term "contacting" has to be understood as previously defined and comprises any possibility of interaction between the potential functional interactor and a neuronal cell. Contacting also comprises the introduction of the potential functional interactor into the neuronal cell which can be effected by a variety of methods including, for example, electroporation, which allows influx of a potential functional interactor contained in the medium surrounding the neuronal cell into the neuronal cell. A neuronal cell that comprises a wt nucleic acid coding for a PRG protein (as indicated in SEQ ID NOs: 1 to 12) can be any neuronal cell capable of neurite movement. The cell may or may not express the wild-type

nucleic acid depending on, for example, the developmental stage of the neuronal cell. For example entorhinal cortex cells of embryonic day 16 (E16), which exhibit neurite movement, do not express PRG-1 while entorhinal cortex cells of postnatal day 0 (P0) do express PRG-1. The choice of either a cell that already expresses or does not express the wild-type nucleic acids will depend on the functional interaction of the potential functional interactor that is sought. If, for example, a functional interactor is sought, that activates transcription within the cell normally not expressing PRG-1 than, for example, an E16 cell could be chosen. If functional interactors are sought that primarily interact on the protein level, i.e. that activate or suppress phosphatase activity of already expressed PRG-1 than neuronal cells expressing PRG-1 would be chosen like, for example, P0 cells.

Bioactive lipid phosphates are lipid phosphates which inhibit neurite movement of neuronal cells, which do not express PRG-1, like for example, E16 cells. Examples of such bioactive lipid phosphates comprise PA, LPA and S-1-P. Whether a lipid phosphate, which can be used in the method of the present invention is bioactive can be determined by, for example, the experiment described in Example 9.

Methods for measuring neurite movements are well-known in the art and are described, for example, in Savaskan et al. (1999) European J. Neurosci. 11:319-326. One way of measuring neurite movement is scoring of the cells after contacting with a bioactive lipid phosphate. It is possible to categorize the cells into at least three different categories, i.e. round cells, cells with short processes and cells with long processes. It is also possible to quantify the effect by measuring the length of the neurite processes. The effect of the potential functional interactor can be determined by comparing the neurite movement of the neuronal cell, the categories the cells are in or the length of the neurite processes after contacting the cell with a bioactive lipid phosphate with or without the functional interactor. Other ways to assess the effect of potential functional interactors are the determination of the expression level of the PRG genes and/or proteins or the enzymatic activity of the proteins.

In a further embodiment the method includes the additional steps of: a) contacting a neuronal cell that comprises a mutant nucleic acid coding for a mutant of the proteins selected from the group consisting of SEQ ID NOs: 1 to 12, a splice variant thereof, or a fragment thereof or that contains a knock-out of the wt nucleic acid coding for one of said proteins

with a potential functional interactor, b) contacting said cell with a bioactive lipid phosphate, and c) measuring neurite movement. The above described neuronal cell is preferably incapable of expressing a functional PRG protein and, thus, can not be stimulated by any functional interactor to activate PRG genes or PRG protein function. Therefore, any potential functional interactor, which shows an effect on the neurite movement of neuronal cells comprising wild-type PRG genes but shows no effect in the neuronal cell comprising mutants or knock-out PGR genes have thereby been shown to functional interact with the PRG genes. Once such an interactor has been identified the mode of functional interaction can be further analyzed and to that end the amount of PRG mRNA and/or protein expressed or the activity of the PRG protein can be determined by a variety of different techniques, which are either known in the art or described herein.

In a preferred embodiment the method of the invention comprises the further steps of: a) modifying the functional interactor to generate a variety of modified functional interactors, b) contacting a neuronal cell comprising a wild-type nucleic acid coding for a protein selected from the group consisting of SEQ ID NOs: 1 to 12, a splice variant thereof, or a fragment thereof and if needed a cell that comprises a mutant nucleic acid coding for a mutant of the protein selected from the group consisting of SEQ ID NOs: 1 to 12, a splice variant thereof, or a fragment thereof with the modified functional interactors, c) contacting said cell or cells with a bioactive lipid phosphate, d) measuring the neurite movement, and e) if needed repeating steps a) to d) for one or more times. The modification of the functional interactor can be any of the modifications outlined above with respect to the modification of an interacting compound and the modification and selection steps can be repeated one or several times until a functional interactor has been selected that shows the desired functional interaction, e.g. repression or activation of the activity in particular of the enzymatic activity of PRG proteins.

In a further embodiment of the method of the present invention the interacting compound identified as outlined above or the functional interactor identified as outlined above, which may or may not have gone through additional rounds of modification and selection, is admixed with suitable auxiliary substances and/or additives. Such substances comprise pharmacological acceptable substances, which increase the stability, solubility, biocompatibility, or biological half-life of the interacting compound or the functional interactor or

comprise substances or materials, which have to be included for certain routs of application like, for example, intravenous solution, sprays, Band-Aids or pills.

Since expression of PRG-1 can prevent LPA induced neurite retraction and/or expression of rat PRG-3 induces neurite extension these proteins have another utility in the treatment of neuronal injuries and diseases. Accordingly a further aspect of the present invention is a pharmaceutical composition for the treatment of neuronal injuries or diseases comprising a protein of the invention, a nucleic acid of the invention, a vector of the invention, a cell of the invention, an antibody of the invention, a binding component isolated by a method of the invention and/or a functional interactor isolated by a method of the invention and if needed suitable auxiliary substances and/or additives.

Accordingly, a further aspect of the present invention is the use of a pharmaceutical composition of the invention for the production of a medicament for the treatment of neuronal diseases or injuries. Neuronal diseases which can be treated with the pharmaceutical composition comprise spinal cord lesion, Alzheimer disease and stroke. Typical neuronal injuries comprise traumata of any sort in particular head traumata resulting in the damage of neurons and in particular the severing of neuronal connections.

As stated above it has also been found that PRG proteins are differentially expressed in certain tissues and that they have been found to be differentially expressed in certain diseases, however, differential expression is also associated with certain disease states. Thus, PRG proteins present attractive targets for diagnosis and treatment of a variety of diseases. Therefore, another aspect of the present invention is the use of the proteins or nucleic acids of the present invention as diagnostic marker for the diagnosis of a disease or disease state, whereby the presence, the absence, or the amount of PRG proteins is evaluated by, for example, immunological methods, RT-PCR, Northern blot. For the immunological detection and/or quantification methods the antibodies of the present invention can be used.

As PRG is differentially regulated in neuronal diseases PRG proteins or nucleic acids are in a preferred embodiment used as diagnostic marker for the diagnosis of neuronal diseases.

Furthermore PRG proteins are overexpressed in tumors. PRG-1, for example, is overexpressed in a variety of tumor cells, e.g. astroglioma WHO Grad III-IV, neuroblastoma, kidney cell carcinoma, myoblastoma and ovarial cell carcinoma, and in particular it has also been found to be overexpressed in migrating, i.e. metastasizing cancer cells which have lost the anchorage dependence for growth. Therefore, PRG proteins also present attractive targets for diagnoses and treatment of tumors, in particular metastasizing tumors. Consequently, a further aspect of the present invention is the use of PRG proteins and nucleic acids of the present invention as a tumor markers and, preferably, as metastatic markers. Because of the above property PRG proteins are also therapeutic targets for the development of drugs, which modulate, preferably inhibit the function of PRG proteins. Such drugs can be identified with above-described methods for identifying interacting or functional interacting compounds.

In a preferred embodiment, PRG proteins of the present invention are used for diagnosis of cancers selected from the group of cancers consisting of neuroblastoma, astroglioma, ovarial cell carcinoma, prostatic cell carcinoma and breast cell carcinoma.

In addition, PRG proteins, in particular PRG-1, have been found to be overexpressed in differentiating sperm cells and, thus, a further embodiment of the present invention is the use of the PRG proteins or nucleic acids as diagnostic targets for the diagnosis of infertility, in which a lack of PRG proteins would indicate either a low amount of differentiating sperm cells or the malfunction of the sperm cells. The amount of expression of PRG proteins or nucleic acids can be detected by, for example, *in situ* immunofluorescence, *in situ* Northern blots. The skilled persons knows a variety of additional methods that are suitable to determine the amount and distribution of PRG proteins and RNA within a cell ansd/or tissue.

The following figures and examples merely serve to illustrate the invention and should not be construed to restrict the scope of the invention to the particular embodiments of the invention described in the examples. All references cited in the text and the disclosure of the priority applications EP 02 020 679.3 and EP 03 002 993.8 are hereby incorporated in their entirety by reference.

Figures

Fig. 1 Panel A depicts the human PRG-1 amino acid sequence (SEQ ID NO. 1). The first 300 amino acids are highly conserved among LPP family members. The other 400 amino acids (gray boxed sequence) of PRG-1 show no homologies to known sequences. The catalytic histidine (His-252) is marked with an asterisk. Panel B depicts rPRG-3 (SEQ ID NO. 11). Start and stop codons are marked with a dark box. Putative transmembrane domains are underlined in grey, the C-terminal tail is indicated light grey. The probes, which were used for *in situ* hybridization are marked with a black line.

Fig. 2 Panel A depicts the hydrophobicity profile of human PRG-1 protein predicted by the Kyte and Doolittle algorithms. The gray shaded area of PRG-1 is predicted as hydrophilic and located in the cytosol. Panel B depicts the hydrophobicity profile of rat PRG-3-protein. The numbers at the bottom of the profiles refer to amino acid residues from the amino terminus. Panel C depicts the *in silico* determined phylogenetic tree of different PRG-proteins and LPP-1.

Fig. 3 Northern blot analysis of PRG-1 mRNA expression

Fig. 4 Expression pattern of PRG-1 mRNA in the developing and lesioned rat brain detected by *in situ* Northern blot. Panel A shows the Toluidene blue staining of a brain section on embryonic day 16 (E16). Panel B shows the *in situ* hybridization signal with a probe specific for PRG-1 mRNA of the same section as shown in panel A. Panel C shows a Toluidene blue staining of a brain section on embryonic day 19 and panel D shows the *in situ* hybridization with a probe specific for PRG-1 mRNA of the same section as shown in panel C. Panels E through K show *in situ* Northern blot analysis of brain sections at days 0, 5, 10, 15, 30 after birth, in an adult and one day after lesion, respectively. The scale bar in E19 equals 850 µm. The scale bar in P30 equals 740 µm and also applies to P0-P15. The scale bar in 1dal equals 500 µm and also applies to adult. "LV" means lateral ventricle, "LP" means lateral posterior thalamic nucleus, "LD" means laterodorsal thalamic nucleus, "bcp" means basal telencephalic plate, posterior part, "CA1" means cornu ammonis, "DG" means dentate gyrus, "RSG" means retrosplenial granular cortex, "dal" means days after lesion.

Fig. 5 Quantification of the *in situ* hybridization signals in different regions of the brain after lesion. "gcl" means granule cell layer, "CA3" means cornu ammonis 3, "CA1" means cornu ammonis and "dal" means days after lesion.

Fig. 6 Overexpression of a PRG-1-eGFP fusion protein in COS-7 cells. Panel A shows the fluorescence of the green fluorescent protein, panel B shows the fluorescence of a fluorecently labeled anti-PRG-1 peptide antibody and panel C shows the co-localization of the fluorescence of the PRG-1-eGFP and the anti-PRG-1 antibody. In each picture the processes of the COS-7 cells are marked with a white arrow. The scale bar depicts a length of 10 µm. Panel D shows the result of a Western blot using an antiserum raised against a C-terminal peptide of PRG-1.

Fig. 7 Immunocytochemical analysis of PRG-1 in the adult rat hippocampus prior and after lesion. Pyramidal neurons are labeled in the CA1 and CA3 region. Polymorphic cells are stained in the hilus. The outermoelcular layer is marked with black errors. "Gcl" means granule cell layer "Oml" means outer molecular layer and "hi" means hilus. The scale bar in panel A and B equals 580 µm. Panel C shows immunoblots from total protein extracts of adult control and deafferentiated hippocampus five days after lesion.

Fig. 8 Panel A shows a higher magnification of the boxed area of panel B of Fig. 7. Immuno-stained axons are marked with black arrows and the terminal branches with white arrows. Panel B shows an electron micrograph of a PRG-1 immunopositive axon. The immunopositive axon is delineated by black arrows, while its terminal branch is delineated by gray arrows. "oml" means outer molecular layer and "ax" means axon and "s" means spine. The scale bar in panel A equals 20 µm and the scale bar in panel B equals 0.4 µm.

Fig. 9 Panel A-C show the result of an RT-PCR analysis of RNA from tissues from E16 and P0 explants. The amplification was carried out with primers specific for PRG-1 (panel A), EDG 2, 4 or 7 (panel B) and β-actin (panel C). Panel D and E depict explants from rat entorhinal cortex at embryonic day 16 and panel F and G depict rat entorhinal cortex at postnatal day 0 (bottom row of panels). Out-

growing axons are marked with white arrows and the panels D and F show neurite retraction in the presence of vehicle (0,9% NaCl) while panels E and G show neurite retraction upon the addition of 100 nmol/l LPA. The scale bar in panel G equals 20 µm.

Fig. 10 Panel A shows the neurite outgrowth length in control cultures (left bar) and LPA treated cultures, (right bar) in E16 and postnatal explants (P0) in µm. Panel B shows the dose-response of LPA on P0 and E16 explants.

Fig. 11 Depicts cell rounding and neurite retraction in response to LPA in N1E-115 cells. The cells depicted in the first three top panels were transfected with a plasmid containing only eGFP and were not treated with LPA but with vehicle only. The cells in the second row were transfected with a plasmid containing only eGFP but were treated with 10 µmol/l LPA, the cells of the third row were transfected with a plasmid coding for a PRG-1-eGFP fusion protein and were treated with 10 µmol/l LPA while the cells depicted in the bottom row of panels were transfected with a mutant PRG-1-eGFP fusion protein, which carried a His-Lys exchange in the catalytic histidine of PRG-1 (PRG-$1^{His/Lys}$) and were also treated with 10 µmol/l LPA. The panels on the left show transfected cells, panels in the middle show nuclear staining (Hoechst staining) and panels on the right show merged images with f-actin staining.

Fig. 12 Panel A shows the quantification of the results shown in Fig. 11 and of a similar experiment performed with wild type N1E-115 cells (wt). Panel B shows the results of RT-PCR using LPA receptor specific primers to assess LPA receptor expression in wild type N1E-115 cells (wt) or PRG-1 transfected N1E cells (PRG-1). Panel C shows the results of RT-PCR using β-actin specific primers to assess β-actin expression in wt N1E-115 cells and in PRG-1 transfected cells. Panel D shows a dose response of LPA treatment on neurite length of PRG-1 overexpression cells. Panel E shows cell viability of N1E-115 cells 48-72 h after transfection. Panel F shows the phosphatase activity of intact cells overexpressing eGFP, PRG-1-eGFP, and PRG-$1^{His/Lys}$.

Fig. 13 Schematic diagram of the proposed axon growth mechanism in a lipid phosphate lipid rich environment. "R" means receptor mediating a retraction signal.

Fig. 14 Depicts the proposed structure of the human PRG-1 wherein those parts presumed to be arranged on the extracellular surface inserted in the plasma membrane and protruding into the cytoplasm are shown.

Fig. 15 Expression pattern of PRG-3 mRNA in the developing rat brain detected by *in situ* Northern blot. Panels A-C depict the in *in situ* staining of rat brain sections at various developmental stages in which E18 and E20 depict stains from embryonic days 18 and 20, and P0, P5, P10, P15 stains post partum at days 0, 5, 10, and 15. The scale bar in A equals 1.8 mm and in panel B 400 µm. Panel D depicts the Northern blot analysis of RNA derived from different tissues of the adult rat.

Fig. 16 Depicts the cellular localization of PRG-3-eGFP fusion proteins. PRG-3 is visible predominantly in the plasma membrane and in neurite extensions. The upper row depicts cells transfected with the peGFP-N1 reporter vector alone and the second and third row cells transfected with a pPRG-3-eGFP fusion construct. The scale bar in the second row represents 2 µm and 5 µm in the third row.

Examples

1. Isolation of PRG-1

Animals and surgery

All animals were housed under standard laboratory conditions, and the surgical procedures were performed in agreement with the German law (in congruence with 86/609/EEC) for the use of laboratory animals. All efforts were made to minimize the number of animals used, and all surgical procedures were performed under sufficient anesthesia to minimize animal suffering. The experimental procedures are described in detail in Bräuer et al (2001) FASEB J. 15:2689-2701.

Substraction cDNA library and differential screening

The SMART cDNA technology from Clontech was used to generate high yields of full-length, double-stranded cDNA from adult, control and lesioned hippocampus rat RNA. To develop the substraction library, the Clontech PCR-Select cDNA substraction Kit (Heidelberg, Germany) was used. Each clone was dotted in duplicates on Hybond N filters (Amersham, Germany) and screened with randomly radioactively labeled cDNA (Prime-A-Gene, Promega, Germany) from adult non-lesioned and lesioned hippocampus.

2. Analysis of the sequence of PRG-1

Similar to other members of LPP-family a hydrophobicity analysis of PRG-1 predicts 6 N-terminal membrane-spanning regions with a highly conserved phosphatase domain. The analysis was done using the DNAsis for Windows Version 2.6; Hitachi Software Engineering Co. Hydrophobicity Analysis Submenue using the Kyte & Doolittle algorithm with all settings set to default values. However, unlike the other members of this family the second type of the protein consists of a long hydrophilic domain of around 400 amino acids (Fig. 2). According to the structural models of LPP orientation in the membrane, this C-terminal extension is positioned on the cytoplasmatic site and might thus play a role as a regulatory or signal transduction domain. Beside the homology of the N-terminal part of the PRG-1 to other members of the LPP-family such as LPP-1 and the Drosophila cell migration modulator Wunen, GenBank searches revealed only one other related gene (genomic DNA sequence: GenBank acc. # NP_011255.11) for which we cloned the complete cDNA sequence and named it PRG-2. This gene shares the same C-terminal extension with partial sequence homology. Thus, these genes represent a novel distinct subclass of the LPP-1 family. Amino acid residues which have been shown to be essential for ectoenzyme activity in the LPP-1 class of proteins are conserved in PRG-1 N-terminal sequences (Fig. 1). Database analysis of the C-terminal domains did not detect any significant similarities to any other protein or any other matches with known conserved domains (using ProDom and Swiss-Prot databases). A GenBank search for orthologous proteins showed that both genes are highly conserved in mammals (human/mouse > 93%), and partial EST sequences indicate orthologous proteins in Xenopus and Zebrafish, whereas no significant homology for the C-terminal part could be found in the Drosophila or other invertebrate genome.

3. Northern blot analysis of PRG-1 expression

20 µg of total RNA from six adult control and six 1 dal animals were loaded on a 1% agarose gel containing formaldehyde, transferred to Hybond™ – Ns (Amersham Life Science, UK) and crosslinked by ultraviolet irradiation. As a probe for PRG-1, the full length cDNA clone as well as the C-terminal coding region was used. As probe for β-actin (as control for mRNA integrity and amounts of mRNA loaded), a cDNA fragment amplified by RT-PCR was used. Primer for the amplification of the control gene β-actin were: β-actin 5' (5'–CAC CAC AGC TGA GAG GGA AAT CGT GCG TGA – 3', SEQ ID No. 25) spanning bases 2395 – 2424, and β-actin 3'-primer (5'–ATT TGC GGT GCA GCA TGG AGG GGC CGG ACT–3', SEQ ID no. 26) complementary to bases 3095 – 3124, with an amplificate length of 520 bp for rat β-actin cDNA (GenBank accession no. J00691). PCR was performed in 25 µl final volume containing 1 mmol/l dNTPs (Pharmacia Biotech, Germany), 2.5 units Taq Polymerase (Perkin Elmer, USA) 2.5 µl 10 x buffer including 2.5 mol/l $MgCl_2$ (Perkin Elmer, USA), 10 µmol/l each primer and 1 µl cDNA using a Thermo-Cycler PTC-100 (MJ Research, Inc., USA). The cycle program was: 95°C, 2 min; 35 x [94°C, 30 s; 70°C, 30 s 72°C, 2 min] and 10 min, 72°C. Both probes were labeled with the Prime-a-Gene Labelling System (Promega, USA) and [^{32}P] dCTP (DuPont NEN, USA). Hybridization was performed in 10 ml hybridization solution (250 mmol/l sodium-phosphate, pH 7.2, 7% SDS, 0.5 mmol/l EDTA, 1% BSA) at 60°C for 12 h. The membrane was washed in 2 x SSC at RT, 0.2 x SSC at RT, and 0.2 x SSC at 40°C for 30 min each. Membranes were exposed to Kodak X-OMAT AR X-ray films at –80°C for 12 h, using an intensifying screen. Northern blot analysis revealed one distinct band which migrated around 5,5 kb. Expression of this mRNA was CNS-specific with the exception of a weak expression in testies (see Fig. 3). Thus, PRG-1 is a novel vertebrate specific protein selectively located in the brain with putative phosphatase function.

4. *In situ* hybridization analysis of PRG-1 expression

For hybridization, an antisense oligonucleotide (5'-GCA GAG GTC TGA ATT CTA GTG TCT ATC GTT ATA GTT CCT TAA CAG TGT GGG-3', SEQ ID No. 27) complementary to bases 425 – 475 of a rat EST cDNA clone (GenBank acc. AW 526088.1) was used. The oligonucleotide was synthesized by Metabion (Munich, Germany). The specificity was confirmed by a BLAST GenBank search to rule out cross-hybridization to other genes. The protocol was used as described by Bräuer et al (2002) *supra*.

The *in situ* hybridization analysis highlighted the tight regulation of PRG-1 transcription in the developing hippocampus. At embryonic day 16 (E16), no PRG-1 transcripts could be detected in the brain (Fig. 4, panel B). An expression signal first appears at day 19 (E19) in the subventricular zone and specifically in the hippocampal anlage, whereas other cortical regions did not show PRG-1 expression (Fig. 4, panel D). From postnatal stages on, PRG-1 mRNA is present in the hippocampus and in the entorhinal cortex throughout adult stages (see Fig. 4, panels E-J). In the dentate gyrus, a region bearing postnatally developing granule cells, weak PRG-1 mRNA expression is found in the infrapyramidal blade at P0, whereas the later developing suprapyramidal blade first showed expression signals at P5. This expression pattern remains unchanged during maturation, however, a reduced expression is apparent in the adult brain.

5. PRG-1 mRNA expression after entorhinal cortex lesion

The treatment of the animals, the surgery the construction of the subtraction cDNA library and the screening were carried out as described in example 1. The *in situ* hybridization was carried out as described in example 4. PRG-1 is upregulated one day after lesion (dal) and peaks at 5 dal in the ipsilateral hippocampus (gcl = 37%, hilus 300%, CA1 = 100%, CA3 = 60%). The contralateral hippocampus (maximum by 1 dal, gcl = 16%, hilus = 200%, CA1 = 59%, CA3 = 46%), as well as the ipsilateral cortex, shows a strong upregulation of PRG-1 mRNA (maximum by 1 dal 83%) (see Fig. 5).

6. Transfection of a PRG-1-eGFP construct

Antibody generation and immunohistochemistry

To design a peptide antibody against PRG-1, a sequence in the hydrophilic C-terminal region was used. The peptide (NH_2-CVGVNGDHHVPGNQ-COOH, SEQ ID No. 28), representing amino acids 490 – 507 of the PRG-1 rat sequence (SEQ ID No. 9), was synthesized by BioGenes (Berlin, Germany). The amino-terminal cysteinyl residue, which is not part of the PRG-1 sequence, was included for conjugation of the peptide to a carrier protein. The peptide was conjugated through the cysteinyl sulfhydryl to maleimide activation (keyhole limpet hemocyanin). Rabbits were immunized by BioGenes. The specificity of the peptide antibody was further tested on Western blot and on brain sections by blocking via peptide incubation prior to adding the antiserum. The protocol for the immunohistochemistry is described in detail by Bräuer et al (2001) Neuroscience 102:515-526.

Western Blot analysis

For Western Blot analysis, rat adult and 5 dal hippocampus extracts were separated on a 12% SDS/PAGE and electroblotted to nitrocellulose membranes (Millipore, Germany). All incubation was done overnight at 4°C in PBST. The PRG-1 antiserum was used at a 1:2000 dilution. Secondary anti-rabbit antibody coupled with horseradish peroxidase was used at a 1:5000 dilution, and visualized by incubation in ECL detection reagents (Amersham Pharmacia, Germany). The protocol for the immunocytochemistry is essentially the same as described in detail in Bräuer et al. (2001) supra].

The immunoblot in Fig. 6D showed a single band obtained by incubation with the anti-PRG-1 antiserum. The absence of specific signal in the preimmune serum prior to immunization is noteworthy. Immunoblots from total protein extracts of adult control and deafferentiated hippocampus shown in Fig. 7C demonstrated an increase five days after lesion (5dal). Data represents three separate experiments in each group. Statistical difference is marked with an asterisk (mean ± S.D.), * $P < 0.05$; Mann-Whitney-*U*-test.

Subcellular localization

PRG-1 tagged with the eGFP reporter gene was used to identify the subcellular localization. Golgi apparatus was visualized with the cell tracker BODYPY ceramide (Molecular Probes, Netherlands). The staining protocol was obtained from molecular Probes.

The transfection studies using a PRG-1 construct tagged with a eGFP reporter gene revealed that PRG-1 protein was processed in COS-7 cells through the Golgi apparatus (data not shown) to its final localization in the plasma membrane of small processes (Fig. 6, panel A). To localize the PRG-1 proteins *in vivo* an antiserum against a peptide from the cytoplasmic C-terminus of PRG-1 was raised. This antiserum specifically stained transfected COS-7 cells, which expressed PRG-1-eGFP fusion proteins (Fig. 6, panel A-C) and detected a specific band in Western blot analysis (Fig. 6, panel B). Both the immunostaining and Western blot signal could be blocked by specific peptide incubation prior to the addition of antiserum (data not shown). The fluorescence of the labeled entire-PRG-1 peptide antibody and the fluorescence of the eGFP part of the fusion protein colocalized in COS-7 cells and in the processes (see white arrows in panels A-C of Fig. 6).

7. Expression analysis by RT-PCR

Tissue from the retraction assays, E16 and P0 explants and N1E-115 cells were used for mRNA isolation and as templates for RT-PCR. cDNA from testis was used as a positive control. The MidiMACS mRNA Isolation Kit (Miltenyi Biotec, Germany) was used to isolate mRNA from the explants or cells. Reverse transcription was performed as described by Bräuer et al. (2000) Hippocampus 10:632-644. PCR was performed with the following primers: PRG-1-5'-primer (5'-CTA GGC TTG TAG CTG TGG GGA ATT TC-3', SEQ ID No. 29), spanning bases 896 bp –921 bp, and PRG-1-3'primer (5'-TCA ATC CTT ATA AGC CCG TGT G-3', SEQ ID No. 30) complementary to bases 2202 bp – 2225 bp with an amplification length of 1329 bp of the PRG-1 cDNA (SEQ ID No. 21). For amplification of the EDG receptor cDNA, the primer EDG-2-5' primer (5'-GAA CTT TGC GAG TGA GCT GG-3', SEQ ID No. 31), spanning bases 836 bp –855 bp, and EDG-2-3'primer (5'TGC GGA GAG CTT TAA CCT CC-3', SEQ ID NO. 32), complementary to bases 1165 bp – 1184 bp with an amplification length of 348 bp of the EDG-2 cDNA (GenBank accession no. NM010336), the primer EDG-4-5'primer (5'-CCT ACC TCT TCC TCA TGT TC-3', SEQ ID No. 33), spanning bases 344 bp – 363 bp, and EDG-4-3'primer (5'-TAA AGG GTG GAG TCC ATC AG-3', SEQ ID No. 34), complementary to bases 1199 bp – 1148 bp of the EDG-4 cDNA (GenBank accession no. NM020028), the primer EDG-7-5'primer (5'-GGA ATT GCC TCT GCA ACA TCT-3', SEQ ID No. 35), spanning bases 673 bp – 693 bp, and EDG-7-3'primer (5'-GAG TAG ATG ATG GG TTC A-3', SEQ ID No. 36), complementary to bases 1096 bp – 1054 bp of the EDG-7 cDNA (GenBank accession no. NM022983). PCR was performed using a Thermo-cycler PTC-100 (MJ Research, Inc.) in 25 µl final volume containing 10 µmol/l dNTPs (Pharmacia, Germany), 2.5 units Taq Polymerase (Stratagen, Germany), 2.5 µl 10 x buffer including 2.5 mol/l $MgCl_2$ (Stratagen, Germany), 10 µmol/l of each primer, and 2 µl of each cDNA for all molecular analysis. For all EDG receptors, as well as for PRG-1 amplification, the cycle program was: 2 min at 95°C, 40 x (94°C, 30 sec; 52°C, 30 sec; and 72°C, 1 min), and 5 min at 72°C. Amplification of β-actin cDNA was performed as described by Bräuer et al. (2000) Hippocampus 10:632-644.

8. Immunocytochemical staining of rat hippocampus

The antibody described in experiment 6 was also used for the immunocytochemical staining and Western blot analysis. For Western blot analysis, rat adult and 5dal hippocampus

extracts were separated on a 12% SDS/PAGE and electroblotted to nitrocellulose membranes (Millipore, Germany). All incubation was done overnight at 4°C in PBST. The PRG-1 antiserum was used at a 1:2000 dilution. Secondary anti-rabbit antibody coupled with horseradish peroxidase was used at a 1:5000 dilution, and visualized by incubation in ECL detection reagents (Amersham Pharmacia, Germany). The protocol for the immunocytochemistry is essentially the same as described in detail in Bräuer et al., 2001 (FASEB J, 15, 2689-2701). The immunocytochemical staining of rat hippocampus revealed that PRG-1 was specifically expressed in neurons (see Fig. 7, panel A) and in particular pyramidal neurons are labeled in the CA1 and CA3 region, polymorphic cells are stained in the hilus and granule cells of the dentate gyrus are also immunopositive. However, the outer molecular layer, the termination zone of afferents from the entorhinal cortex (Skutella T. and Nitsch R. (2001) Trends. Neuroscience 24:107-163) showed no PRG-1 positive fibers (Fig. 7, panel A). Conversely five days after entorhinal cortex lesion, a clear immunoreactive PRG-1 positive band appeared in the denervated outer molecular layer (Fig. 7, panel B). Western blot analysis revealed a 50% increase in PRG-1 expression in the denervated hippocampus (Fig. 7, panel C). PRG-1 immunostaining highlighted single axonal processes in the outer molecular layer which form terminal branches (Fig. 8, panel A). The higher magnification of an area from the immuno stained axons showed that PRG-1 is indeed localized in the growth cone-like axon structures in the denervated zones of the hippocampus (see Fig. 8, panel B).

Subcellular localization

PRG-1 tagged with the eGFP reporter gene was used to identify the subcellular localization. Golgi apparatus was visualized with the cell tracker BODYPY ceramide (Molecular Probes, Oregon). The staining protocol was obtained from Molecular Probes.

9. Effect of PRG-1 expression on the LPA response of neurons

LPA induced neurite retraction in explants

Entorhinal explants from E16 and P0 rat pups were obtained from timed-pregnant Wistar rats and were cultivated as described (N. E. Savaskan (2000) Eur. I. Neurosci 12:1024-1032). In brief, entorhinal cortex was carefully dissected from the hippocampal anlage and the meninges were removed. Explants were gently transferred with a fire-polished Pasteur pipette into 12-well plates and cultivated on baked glass cover slides coated with laminin

and poly-L-lysin (25 µg/ml and 10 µg/ml, respectively) in culture medium containing selenium-defined fetal bovine serum [5%] (N. E. Savaskan et al (2000) FASEB J. e-published) (Neurobasal medium plus 25 µg/ml Penicillin/Streptomycin; B-27 supplement). After 24 h, culture medium was exchanged and cultivation was further performed in serum-free Neurobasalmedium for 20 h. Serum-starved explants were treated with 100 nmol/l oleoyl-LPA (5 mmol/l stock solution in ultra-filtrated water) for 10 min or with vehicle (0,9% NaCl) and then fixed in 4% paraformaldehyde for 20 min. For F-actin staining, fixed tissues were incubated with TRITC-phalloidin (0.1 µg/ml, Sigma, Germany) for 40 min, followed by incubation with HOECHST 33258 dye (1:20,000, Sigma, Germany) for 5 min at room temperature. After three washing steps in PBS, explants were coverslipped with Immuno-Mount (Merck, Germany) prior to analysis. Images were taken with a CCD camera on an Olympus BX-50 microscope and quantification was performed using the Meta Morph analysis system (Universal Imaging, PA). For statistical analysis Statview II was used (Abacus, USA).

A dose response of LPA neurite length of E16 and P0 explants was done as described above, however, with 0, 0.1, 1.0 and 10 µmol/l.

Entorhinal explants obtained at day 16 (E16) do not express PRG-1 while postnatal explants (P0) express PRG-1(see Fig. 9, panel A). In contrast, the LPA-specific receptors EDG-2/4/7 were equally expressed in both embryonic and postnatal explants (see Fig. 9B). The control RT-PCR with β-actin showed the integrity of the RNA from E16 and P0 cells. Both embryonic and postnatal explants grow equally well under serum-free culture conditions and show long extending axons (see Fig. 9, panels D and F). However, their response to LPA differed dramatically (see Fig. 9, panels E and G). Whereas application of 100 nmol/l LPA led to rapid neurite retraction in embryonic entorhinal explants (E16; n = 20, compare panel D to panel E), postnatal explants (P0; n = 22, compare panel F to panel G) did not differ significantly from vehicle treated control cultures. Thus, postnatal entorhinal axons expressing PRG-1 are resistant to LPA-induced neurite retraction. The amount of retraction observed in panels D-G is quantified in Fig. 10, panel A. The dose response is shown in Fig. 10, panel B.

10. Differential effect of PRG-1 and PRG-1 mutant on LPA-induced neurite retraction

Site-directed mutagenesis of PRG-1$^{HIS/LYS}$

The rat PRG-1 full length clone was amplified by Marathon PCR (Clontech, USA) from adult rat hippocampus RNA (SEQ ID No. 17). For transfection studies, the full length PRG-1 coding sequence was fused to EGFP (pEGFP-N1 vector Clontech, USA). The PRG-1$^{His/Lys}$ exchange mutant at the catalytic histidine (His-252) was introduced in the same protein fusion vector by site specific mutagenesis (CAT to AAG).

LPA induced neurite retraction and protection in N1E-115 cells

N1E-115 mouse neuroblastoma cells (ATCC: CRL-2263) were routinely grown in DMEM medium supplemented with selenium-defined fetal bovine serum (10%). The cells were seeded on baked glass cover slides at a density of 10,000 cells/cm^2. The next day, cells were transfected with the cationic lipids procedure (FuGene6, Roche, Germany) and cultivated for 24 h. Serum-starvation was performed for 20 h in DMEM medium, followed by treatment with 10 µmol/l oleoyl-LPA or vehicle (0.9% sodium chloride) (K. Jalink et al (1993) Cell Growth Differ. 4:247-255). After 10 min, cells were fixed in 4% paraformaldehyde for 20 min at room temperature and further analysis processed as described above. Images were taken with a CCD camera on an Olympus BX-50 microscope. Quantification was performed with the Meta Morph analysis system (University Imaging, PA). For statistical analysis Statview II was used (Abacus, USA). The effects of transfection on cell viability were analysed by MTT assay and propidium iodide staining (Savaskan N.E. et al. (2002) FASEB J. 17:112-114).

N1E-115 cells are uniformly sensitive to LPA-induced growth cone collapse (see Fig. 11 and compare first row of panels versus second row of panels). This is also confirmed by phalloidin staining (K. Jalink et al, (1994) J. Cell Biol. 126:801-810) which showed actin polymerization upon PRG-1 overexpression, however, led to a resistance of N1E-115 cells to LPA-induced growth cone collapse and also prevented LPA-induced actin-polymerization (see Fig. 11, third row of panels). The mutation of the conserved catalytic histidine (His-252) to a lysine (PRG-1$^{His/Lys}$) a change which has been shown to completely abolish enzymatic function of the catalytic center of LPP-1 (N. Zhang, et al. (1997) *supra*) no longer prevented LPA-induced retraction of processes as achieved by the wt-construct. This shows that the conserved enzymatic domain of the LPP-1 family is necessary for PRG-1 function in attenuating LPA-induced neurite retraction. The results of the experiments are quantified in Fig. 12, panel A. The transfection, however, had no effect on the

expression of the LPA-receptors EDG-2/4//7 (see Fig. 12, panel B). The control for the integrity of the RNA tested by RT-PCR is shown in Fig. 12, panel C. The resistance against CPA-induced growth cone collapse achieved by PRG-1 overexpression could only be overcome by a 10-fold increase of LPA applied to the culture (Fig. 12, panel D).

11. Ectophosphatase activity in PRG-1 transfected N1H-115

The assay procedures used were adapted from those described in Imai et al. (2000) J. Clin. Endocrinol. Metab 85:3370-3375 and Hooks S.B. et al. (2001) J. Biol. Chem. 276:4611-4621. Briefly, transfected cells were harvested after serum-free cultivation for 20 h by scraping in lysis buffer (containing 20 mmol/l HEPES pH 7.4, 1 mmol/l $NaHCO_3$, 500 µmol/l DTT, 1 mmol/l EGTA) and sonicated with two strokes (Bandolin GM 70, Germany). After centrifugation at 800 x g, the supernatant was diluted in lysis buffer and centrifuged at 100,000 x g for 1 h. Alternatively, the supernatant was topped on a sucrose step gradient (50% and 5%) and centrifuged at 100,000 x g for 1 h (Savaskan, N.E. et al. (2000) Eur. J. Neurosci. 12:1024-1032. The resulting pellet and interphase, respectively, were re-homogenized and centrifuged again at 100,000 x g for 1 h. The crude membrane pellet was re-suspended in reaction buffer (50 mmol/l HEPES pH 7,5; 1 mmol/l EGTA) and protein concentration was determined spectroscopically by Bradford protein assay (Amersham, Germany). Assessment of LPA metabolism was performed with exogenous ^{3}H-oleoeyl-LPA (Perkin Elmer, Germany) measuring ^{3}H-oleoeyl-glycerol production. Briefly, 10-25 µg membrane proteins were pre-warmed to 37°C in reaction buffer and reactions were started by the addition of 10 µmol/l ^{3}H-oleoeyl-LPA. The reaction was allowed to proceed for 5-30 min at 37°C and stopped with the addition of 2.5 vol acidified methanol and 1.5 vol chloroform. After two-phase separation, the chloroform phase was dried under N_2 and applied to silica gel matrices (Machery Nagel, Germany). Plates were developed in chloroform-aceton-acetic acid (90:10:1). All fractions of dried plates were scintillation counted and compared with authentic standards (LPA, 1-monoolein, 1,2-monoolein, oleic acid). All experiments were performed in triplicate. The ecto-phosphatase assay in intact cells was determined as described above. ^{3}H-LPA was added to the serum-free medium and the reaction was allowed to proceed for 5-60 min. The reaction was stopped by adding 2.5 vol acidified methanol and 1.5 vol chloroform to the supernatant. The radioactivity was determined in the lipid fraction as described above.

The results from three independent sets of experiments are shown in Fig. 12, panel F (one set with n = 40 for each group in the outgrowth assay). PRG-1-eGFP showed essentially the same ecto-phosphatase activity as the wt PRG-1 construct. Statistical differences from controls are marked with an asterisk (mean ± S.D.), $***P < 0.001$; two-tailed t test with Bonferroni correction for multiple comparisons.

The extracellular LPA-degradation achieved by transfected N1E-115 cells revealed a 5-fold increase in ecto-phosphatase activity of wildetype PRG-1 transfectants when compared to eGFP transfection alone (Fig. 12, panel F). Moreover, point-mutation in the conserved catalytic domain by His/Lys exchange led to a 95 % decrease of ecto-phosphatase activity (Fig. 12, panel F). These findings show that PRG-1 has ecto-phosphatase activity which is conveyed by a conserved enzymatic domain present in the LPP-1 family, and necessary for attenuating LPA-induced neurite retraction. In addition transfection of the PRG-1 construct into N1E-115 cells did not prevent CPA-induced retraction of processes as achieved by the wt-constructs, whereas cell viability was unaffected (see Fig. 12, panel E).

Thus the ecto-phosphatase activity of PRG-1 was shown by two independent experiments: a) transfection of a mutant construct into N1E-115 cells did not prevent LPA-induced retraction of processes as achieved by transfection of wt construct and b) the transfection of the wt construct led to a 5-fold increase in ecto-phosphatase activity, if compared to cells transfected with a control vector.

12. Model of axon growth mechanism

Fig. 13 shows a diagram of the proposed axon growth mechanism in a phospholipid rich environment. Axons that are sensitive to repulsive phosphor lipid but do not express PRG-1 are unable to cross a phosphor lipid-rich barrier. In contrasts PRG-1 expressing neurons can grow through a phosphor lipid rich zone by local depleting the extracellular pool of repulsive phosphor lipids acting as ligands on EDG-receptors. This way, PRG-1 may regulate the activation of EDG-receptors and thereby modulate axonal outgrowth.

13. Northern blot analysis of PRG-3 expression

The full coding region of PRG-3 was amplified by PCR and the product was p32-dCTP labelled by T4 kinase reaction. Hybridization was performed overnight at 68°C and expo-

sure followed for 20h. The multi-tissue Northern blot analysis of rat PRG-3 mRNA shows a single 2,4 kb band in brain and liver. Slightly lower bands are also present in kidney and testis as depicted in Fig. 15.

14. *In situ* hybridization analysis of PRG-3 expression

For hybridization, we used two antisense oligonucleotides which both gave essentially the same hybridization signal: 5'-GCA GAG GTC TGA ATT CTA GTG TCT ATC GTT ATA GTT CCT TAA CAG TGT GGG-3' (SEQ ID NO. 37) and 5'- CAT CCT TCT GTA GTA GCT TTC TGC CTC TGC CTC CAC TTC TCT CT -3' (SEQ ID NO. 38) complementary to rat PRG-3 sequence (SEQ ID NO. 23). The oligonucleotide was synthesized by Metabion (Munich, Germany). The specificity was confirmed by a BLAST GenBank search to rule out cross-hybridization with other genes. We used the protocol as previously described (Brauer et al., 2001, supra).

Kainate administration and assessments of seizure activity and neuronal cell death in vivo

Six rats, weighing 200-300 g, were weight-paired (± 10 g per pair). These animals received a single i.p. injection of kainic acid (10 mg/kg bodyweight; from Ocean Products Int., Canada) freshly dissolved in 0.9 % saline. Behavior was then observed constantly for 24 hr via video time lapse recordings. Controls received a single i.p. injection of saline in the same volume or were not treated . Severity of seizures was scored for 4 h after kainate injection using the classification of Zhang et al. Twenty-four hours after kainate injections, rats were killed and brains were harvested. Coronal brain sections were cut on a freezing microtome with 20 µm thickness and stained with cresyl violet and acid fuchsin. Nissl-positive undamaged neurons were counted in five coronal brain sections per animal (sections were chosen by unbiased sampling), and the mean number of cells per section were determined such that the value obtained for each rat represents an average total number of neurons counted per section (250 µm by 250 µm square in the middle of the CA1 region). Counts were performed by an investigator blind to treatment status.

The hybridization was carried out as described above. At embryonic day 16 (E16) a hybridization signal for PRG-3 can be detected in the hippocampal anlage, thalamus, and in the olfactory bulb. At perinatal stages (E20 – P0), a strong hybridization signal is found in the cortex and hippocampus except the dentate gyrus (dg). Fig. 15, panel B shows a higher

magnification of the hippocampus. Note that in the dentate gyrus the first hybridization signal occurs at postnatal day ß (P0). Fig. 15, panel C shows that adult, PRG-3 transcripts can be found in all principal layers of the hippocampus. A rapid PRG-3 repression is found six hours after kainic acid application. Five days after kainic acid application, PRG-3 mRNA shows comparable levels to the adult non-treated controls. CA, cornu ammonis; cb, cerebellum; Cx, cortex; dg, dentate gyrus; KA, kainic acid. Scale bar in A, is 1.8 mm and in B, 400 µm.

15. Effect of PRG-3 expression on neurons

N1E-115 cells were transfected with peGFP-N1 reporter vector alone or with a pPRG-3-eGFP fusion construct as descried above. As can be seen from the second and third row the eGFP is mainly found in the cytosol whereas PRG-3-eGFP is localized in the plasma membrane and in neurite extensions (arrows). Note that PRG-3-eGFP expression induce a spreading-like phenotype and long extensions. Scale bar in the second row of panels represents 2 µm; in the third row of panels 5 µm.

16. PRGs as a prognostic marker for cancer

To test the hypothesis, that PRG-1 might be a prognostic marker for cancer diagnostics, differential human prostatic tumors were screened by means of PCR and immunocytochemistry. Adenocarcinoma is the most malignant neoplasia of human males in western world. Samples from 10 matched pairs of microdissected prostate tissue (tumor and normal) were frozen and sections were made. A transcription analysis was performed using RNA preparations from these samples. It was found, that in normal prostate tissue almost no PRG-1 transcript or protein could be detected. In tumor tissue with Gleason tumor grades 1-3, which is characterized as low-grade tumors, we found only 2 PRG-1 positive samples. Analysis of high-grade tumors (Gleason grade 4-5) revealed in 80% of the cases a significant PRG-1 upregulation. Therefore, PRG-1 is an independent prognostic marker for high-grade prostate tumors in human males.

17. PRG as a prognostic marker for Alzheimer's disease

Alzheimer's disease is characterized by intracellular neurofibrillary tangle formation formed by tau-based paired helical filaments (PHF) and by extracellular beta-amyloid plaques. The degree of Alzheimer dementia correlates well with the severity of PHF occurrence. These PHF are formed by hyperphosphorylated tau formation. Analysis of brain

sections from patients with Alzheimer's disease revealed a reduced PRG-1 expression. To gain insights into the functional role of PRG-1 in Alzheimer's pathology we used an established cell culture model.

Comparing neurons overexpressing PRG-1 with control transfected cells revealed an significant reduction of hyperphosphorylated tau protein. Also, using okadaic acid or LPA as known tau hyperphosphorylation induced substances, we found a significantly decrease in hyperphosphorylated tau and PHF formation.

Claims

1. Isolated protein comprising the same or substantially the same amino acid sequence selected from the group consisting of SEQ ID NOs: 1 to 12, or a splice variant or a salt thereof.

2. Protein according to claim 1, which comprises at least one fragment of said amino acid sequences.

3. Nucleic acid, which comprises at least one nucleic acid encoding a protein according to claims 1 and/or 2.

4. Nucleic acid according to claim 3, which consists of DNA or RNA.

5. Nucleic acid according to claim 4 comprising a nucleic acid selected from the group consisting of SEQ ID NOs: 13 to 24.

6. Nucleic acid according to one of claims 3 to 5 further comprising at least one promoter, enhancer, intron and/or polyA-sequence.

7. Nucleic acid, which is complementary to the nucleic acid according to one of claims 3 to 6.

8. Vector comprising a protein according to claims 1 or 2 and/or a nucleic acid according to one of claims 3 to 7.

9. Vector according to claim 8 selected from the group of vectors consisting of plasmids, phagemids, phages, cosmids, artificial mammalian chromosomes, knock-out or knock-in constructs, viruses, in particular adenovirus, vaccinia virus, baculovirus, retrovirus, adeno-associated-virus, rhinovirus, HIV, adeno-associated virus (AAV), herpes simplex virus (HSV-1), lentivirus, filovirus and engineered versions thereof, naked DNA, virosomes, liposomes, nucleic acid coated particles, in particular gold spheres.

10. Isolated cell comprising a protein according to claims 1 or 2, a nucleic acid according to claims 3 to 7 and/or a vector according to claims 8 or 9.

11. Cell according to claim 10, which is a stem cell, a neuronal precursor cell or a neuronal cell, in particular an axon.

12. Transgenic non-human animal generated from a cell according to claims 10 or 11.

13. Antibody directed against a protein according to claims 1 or 2.

14. Method of producing a protein according to claims 1 or 2 and/or a nucleic acid according to claims 3 to 7 comprising the steps of:

a) cultivating a cell according to claims 10 or 11, and
b) isolating said protein and/or said nucleic acid.

15. Method of isolating compounds interacting with a protein according to claims 1 or 2 comprising the steps of:

a) contacting said protein with at least on potentially interacting compound,
b) measuring binding of said compound to said protein.

16. Method according to claim 16, further comprising the steps of:

a) selecting a binding compound,
b) modifying the binding compound, to generate a variety of modified binding compounds,
c) contacting said protein with each of the modified binding compounds,
d) measuring binding of said modified compounds to said protein, and
e) if needed repeating steps a) to d) for one or more times.

17. Method of isolating functional interactors comprising the steps of:

a) contacting a neuronal cell that comprises a wt nucleic acid coding for a protein selected from the group consisting of SEQ ID NOs: 1 to 12, a splice variant thereof, or a fragment thereof with a potential functional interactor,
b) contacting the cell with a bioactive lipid phosphate, and
c) measuring neurite movement.

18. Method according to claim 17 further comprising the steps of:

a) contacting a neuronal cell that comprises a mutant nucleic acid coding for a mutant of the protein selected from the group consisting of SEQ ID NOs: 1 to 12, or a splice variant thereof or that contains a knock-out of the wt nucleic acid coding for one of said proteins with a potential functional interactor,
b) contacting said cell with a bioactive lipid phosphate, and
c) measuring neurite movement.

19. Method according to claims 17 or 18 further comprising the steps of:

a) selecting a functional interactor,
b) modifying the functional interactor, to generate a variety of modified functional interactors,
c) contacting a neuronal cell as used in claim 17 a) and if needed a cell as used in claim 18 a) with each of the modified functional interactors,
d) contacting said cell or cells with a bioactive lipid phosphate,
e) measuring neurite movement, and
f) if needed repeating steps a) to d) for one or more times.

20. Method according to one of claims 15 to 19, further comprising the step of admixing the interacting compound or the functional interactor with suitable auxiliary substances and/or additives.

21. Pharmaceutical composition for the treatment of neuronal injuries or diseases comprising a protein according to claims 1 or 2, a nucleic acid according to claims 3 to 7, a vector according to claims 8 to 9, a cell according to claims 10 to 11, an antibody according to claims 13, a binding compound isolated by the method of claims 15 or 16

and/or a functional interactor isolated by the method of claims 17 to 19 and if needed suitable auxiliary substances and/or additives.

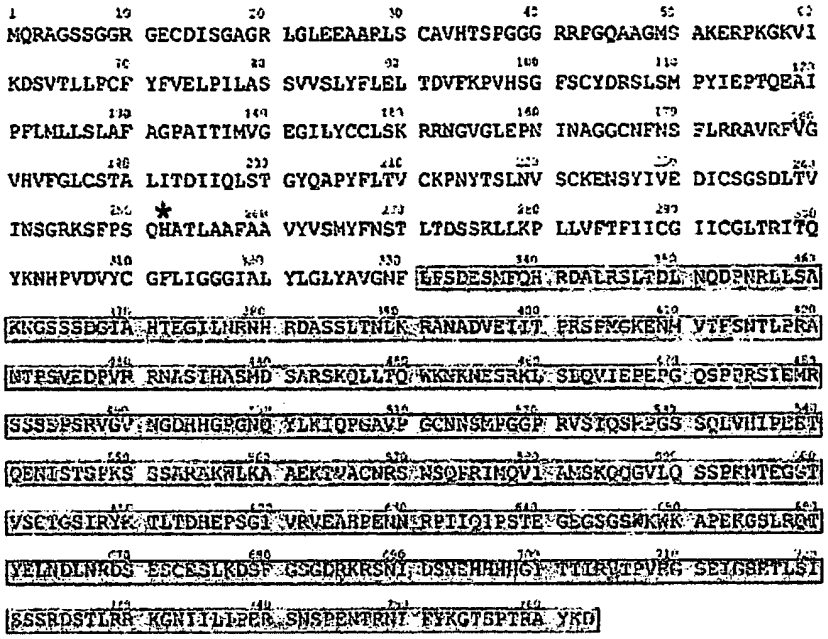
22. Use of a pharmaceutical composition of claim 21 for the production of a medicament for the treatment of neuronal diseases or injuries, including spinal card lesions, head traumata, Alzheimer disease and stroke.

23. Use of a protein according to claim 1 or 2 or a nucleic acid according to claims 3 to 7 as a diagnostic marker for the diagnosis of a disease or disease state.

24. Use according to claim 23, where the disease is a neuronal disease, a tumor disease or infertility.

Figure 1

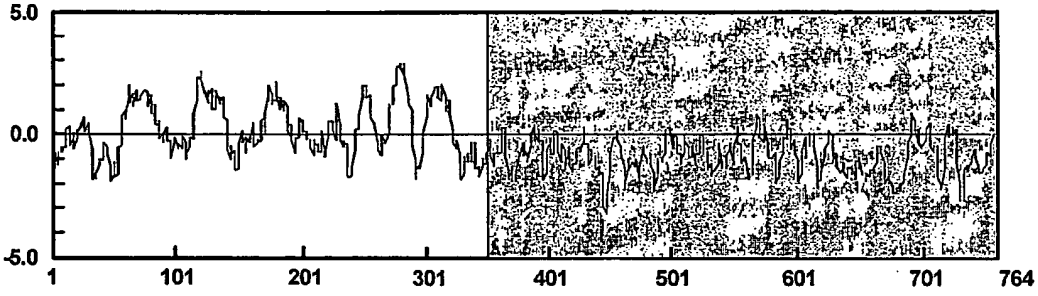
A



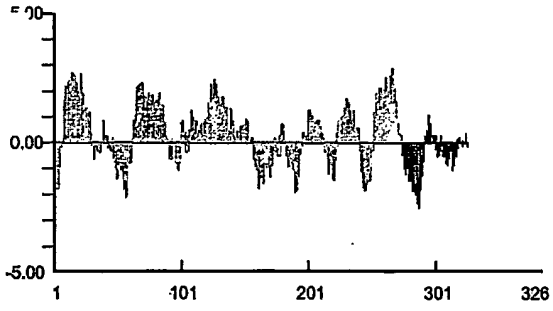
B

Figure 2

A


5.0
0.0
-5.0
1
101
201
301
401
501
601
701
764

B


0.00
-5.00
1
101
201
301
326

C

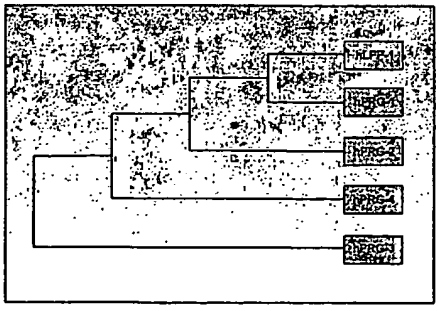


Figure 3

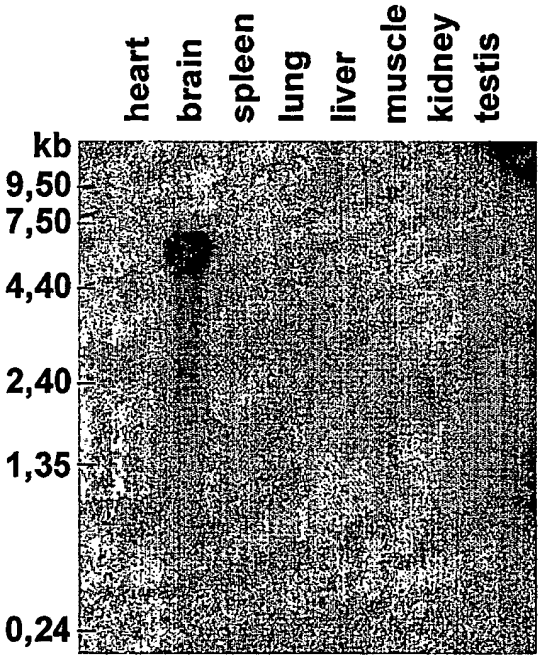

heart
brain
spleen
lung
liver
muscle
kidney
testis
kb
9,50
7,50
4,40
2,40
1,35
0,24

Figure 4

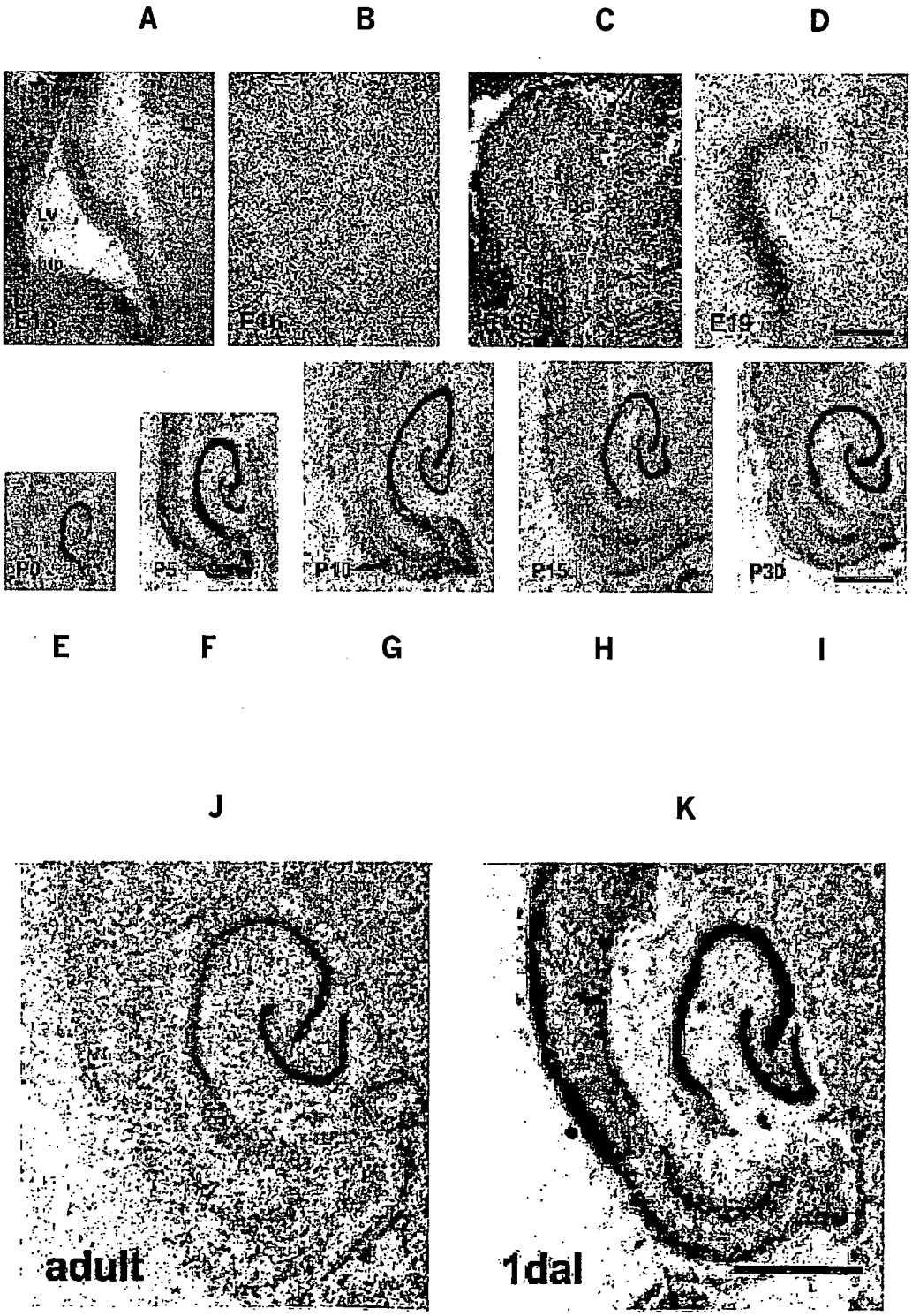


Figure 5

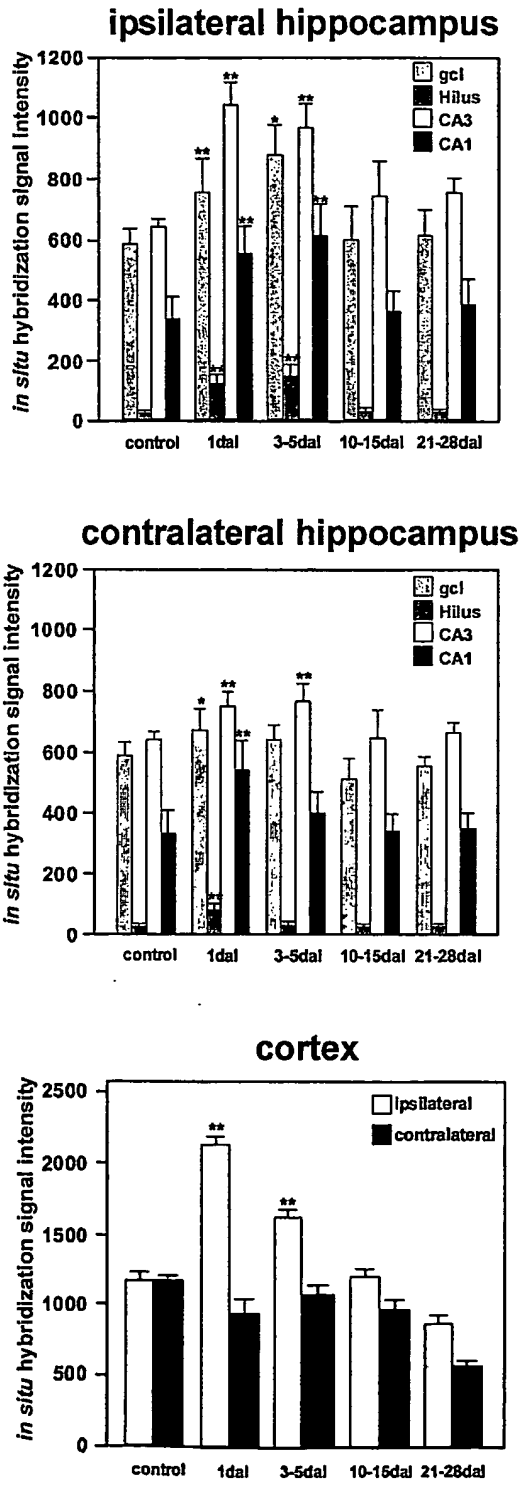

ipsilateral hippocampus
in situ hybridization signal intensity
1200
1000
800
600
400
200
0
gcl
Hilus
CA3
CA1
control
1dal
3-5dal
10-15dal
21-28dal
contralateral hippocampus
in situ hybridization signal intensity
1200
1000
800
600
400
200
0
gcl
Hilus
CA3
CA1
control
1dal
3-5dal
10-15dal
21-28dal
cortex
in situ hybridization signal intensity
2500
2000
1500
1000
500
0
ipsilateral
contralateral
control
1dal
3-5dal
10-15dal
21-28dal

Figure 6

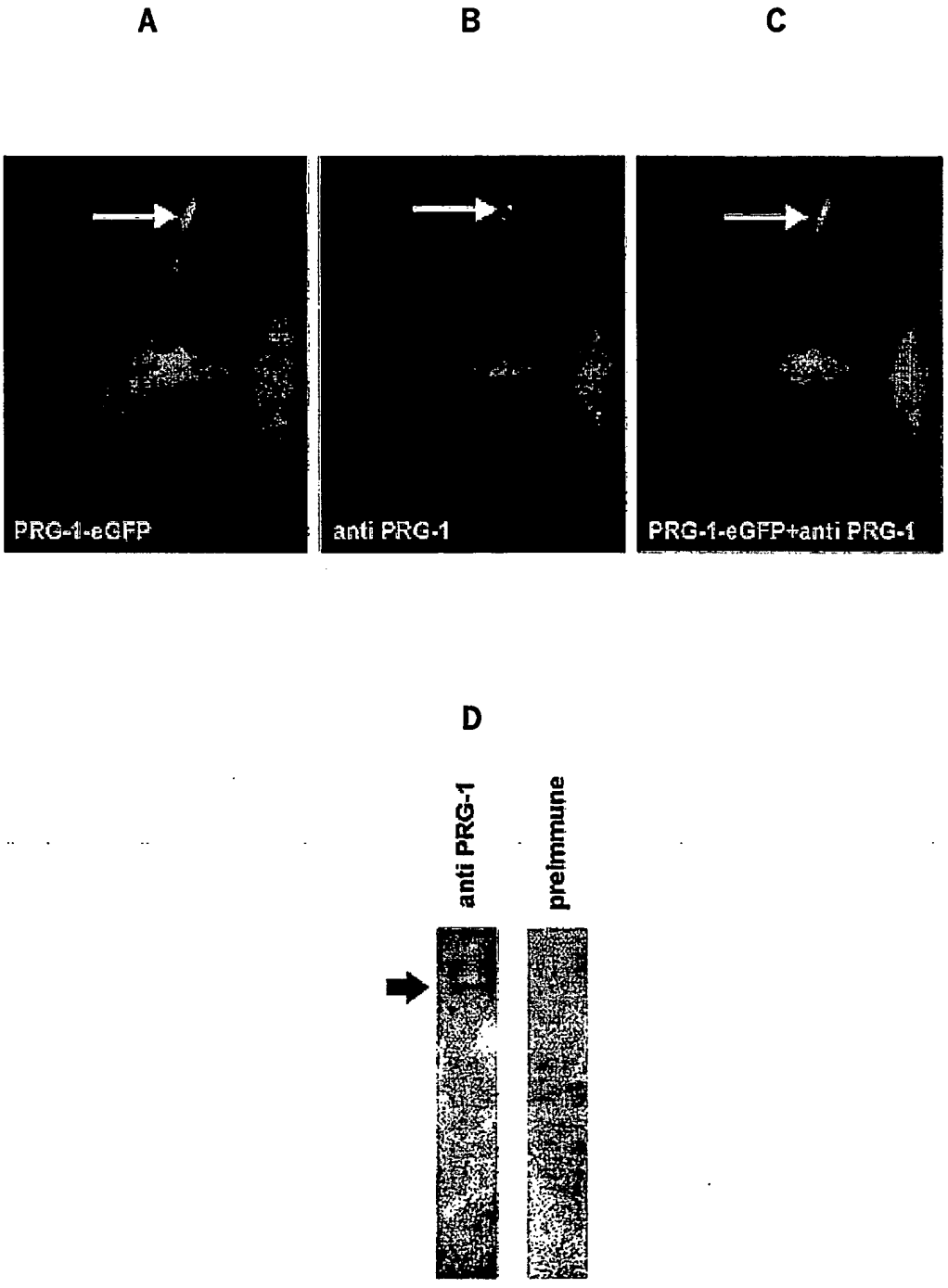
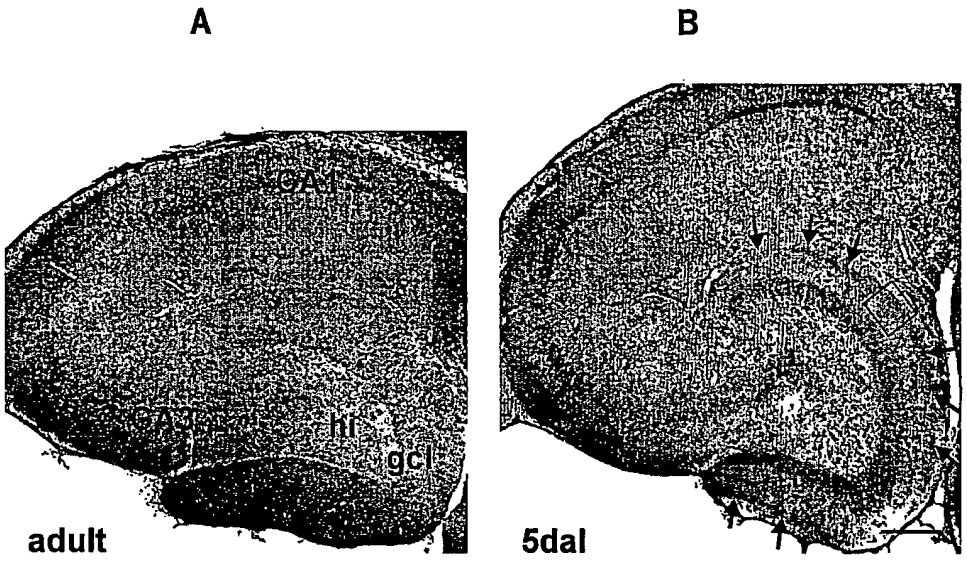

A
B
C
PRG-1-eGFP
anti PRG-1
PRG-1-eGFP+anti PRG-1
D
anti PRG-1
preimmune

Figure 7


A
B
CA1
hl
gc
adult
5dal

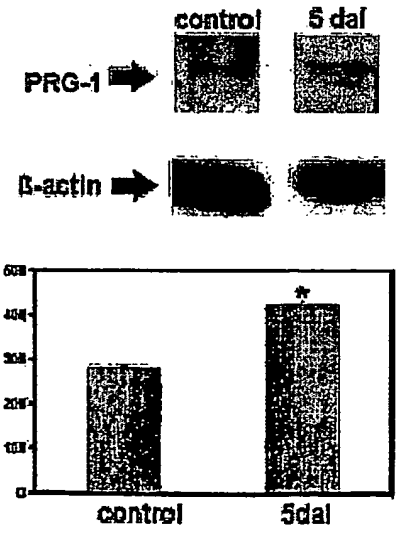

C
control
5 dal
PRG-1
β-actin
*
control
5dal

Figure 8

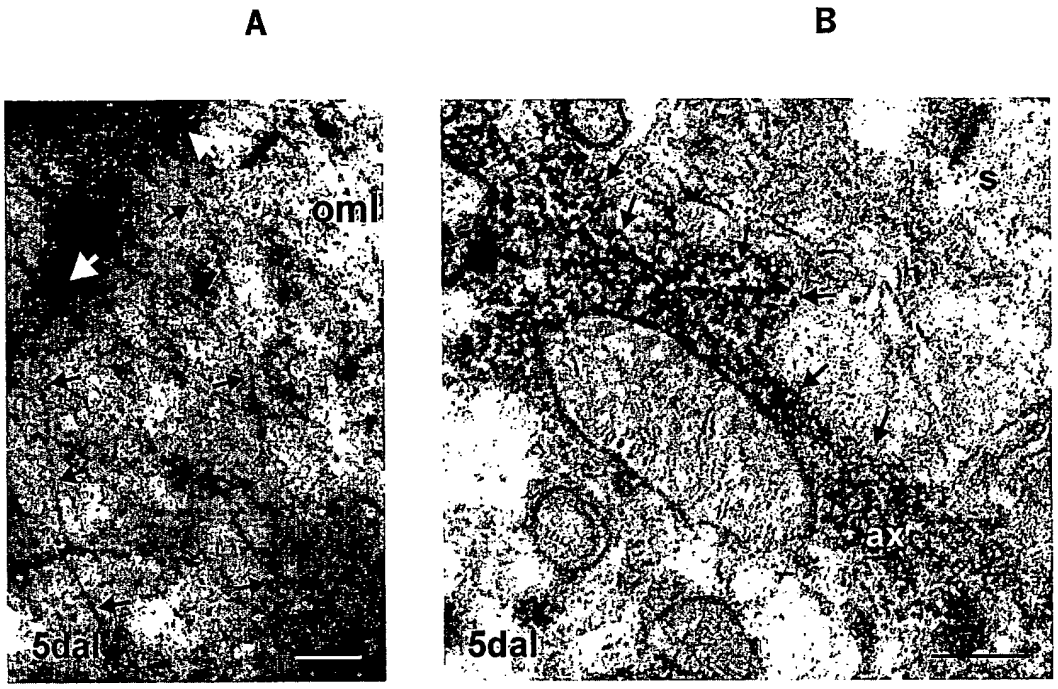


Figure 9

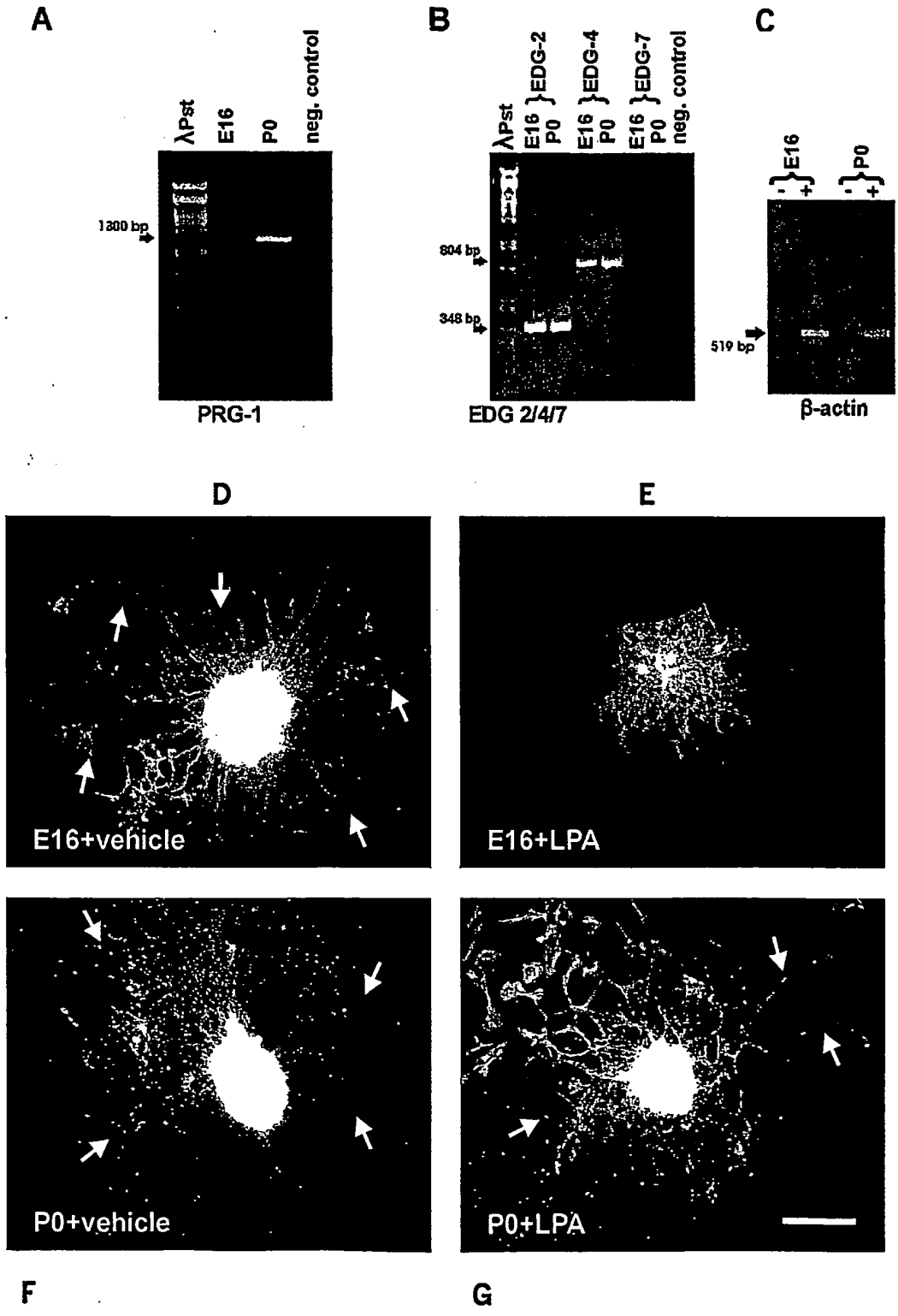
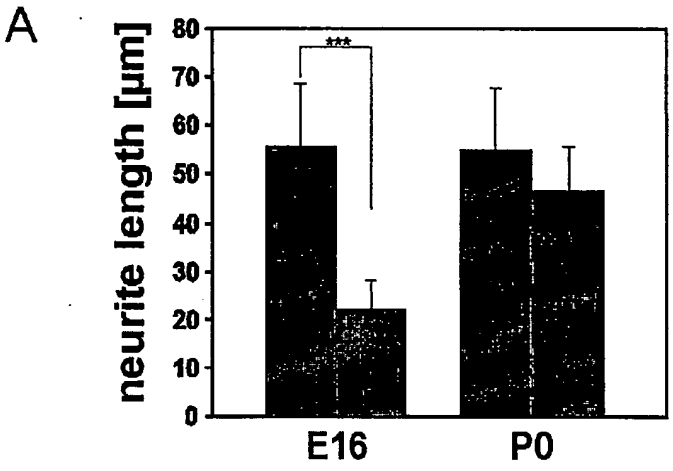

A
λPst
E16
P0
neg. control
1300 bp
PRG-1
B
λPst
E16
P0
EDG-2
E16
P0
EDG-4
E16
P0
EDG-7
neg. control
804 bp
348 bp
EDG 2/4/7
C
E16
P0
519 bp
β-actin
D
E16+vehicle
E
E16+LPA
P0+vehicle
P0+LPA
F
G

Figure 10


A
neurite length [µm]
80
70
60
50
40
30
20
10
0
***
E16
P0

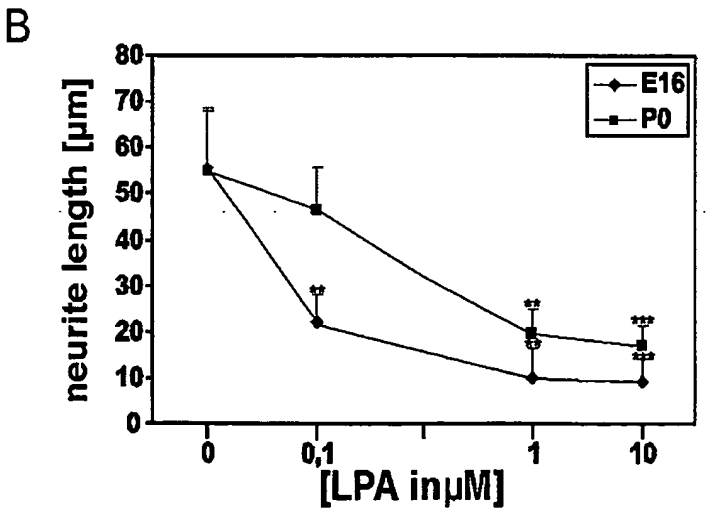

B
neurite length [µm]
80
70
60
50
40
30
20
10
0
E16
P0
0
0,1
1
10
[LPA inµM]

Figure 11

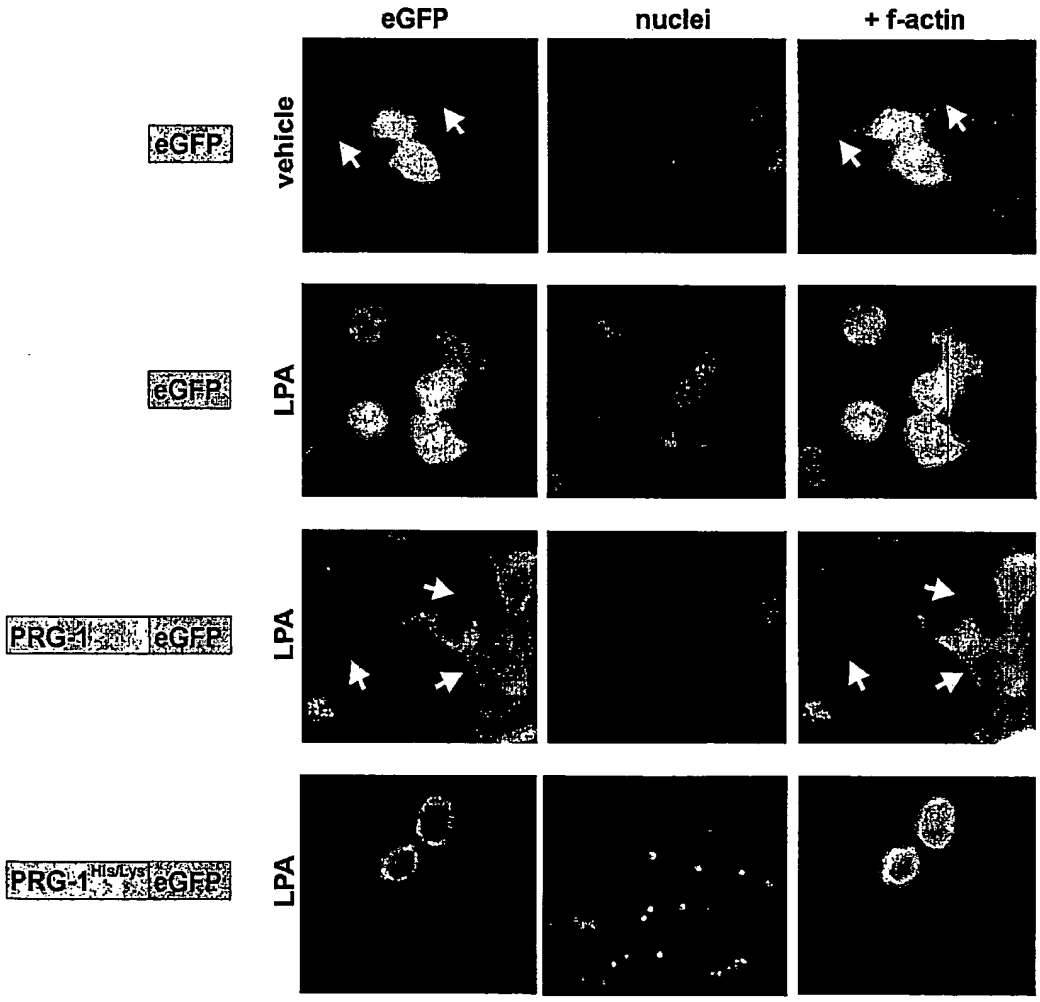

eGFP
nuclei
+ f-actin
vehicle
LPA
LPA
LPA
eGFP
eGFP
PRG-1
eGFP
PRG-1
His/Lys
eGFP

Figure 12

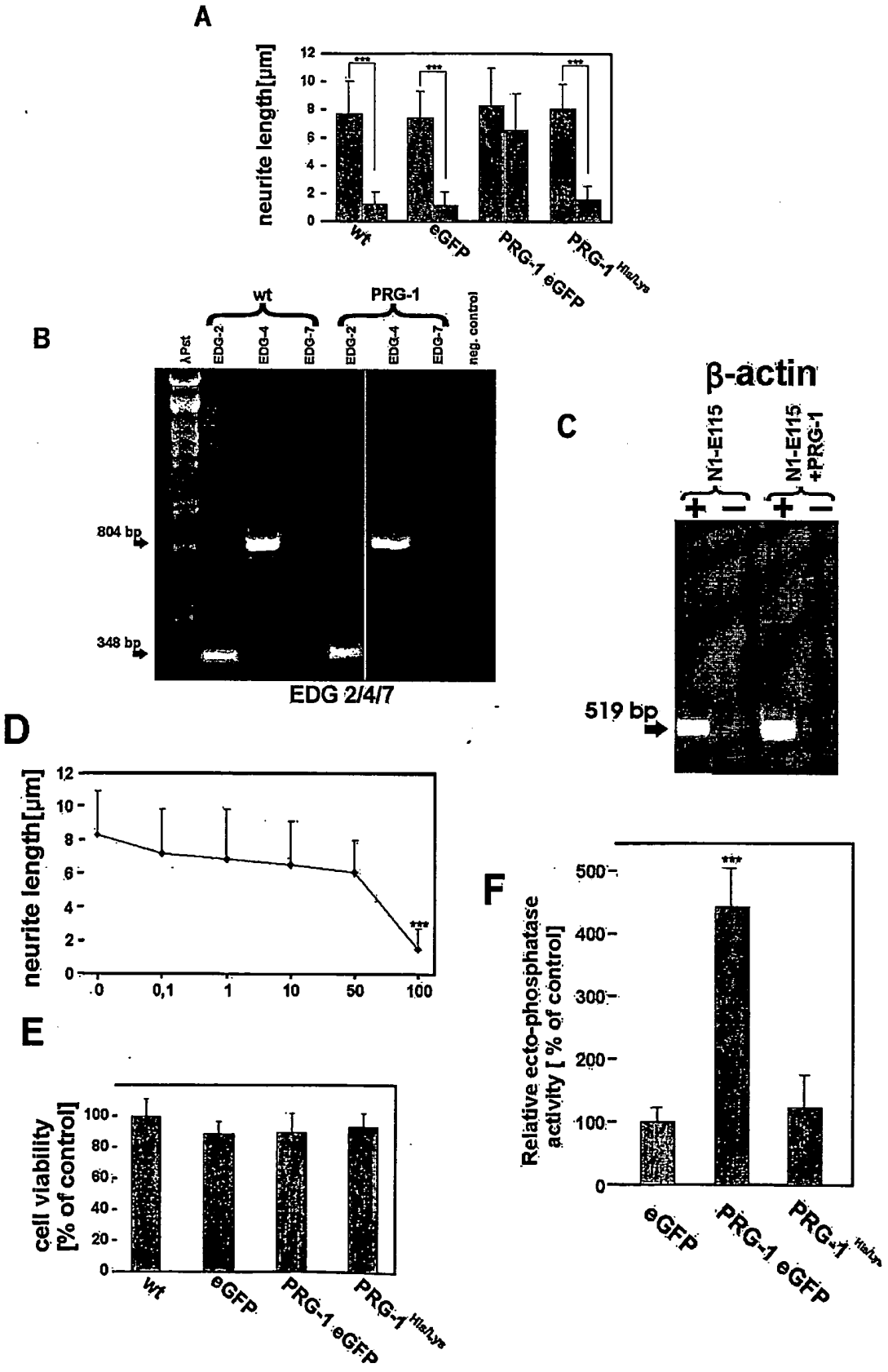

A
neurite length[µm]
wt
eGFP
PRG-1 eGFP
PRG-1 His/Lys
B
wt
PRG-1
λPst
EDG-2
EDG-4
EDG-7
neg. control
804 bp
348 bp
EDG 2/4/7
C
β-actin
N1-E115
N1-E115 +PRG-1
519 bp
D
neurite length[µm]
E
cell viability [% of control]
F
Relative ecto-phosphatase activity [% of control]

Figure 13

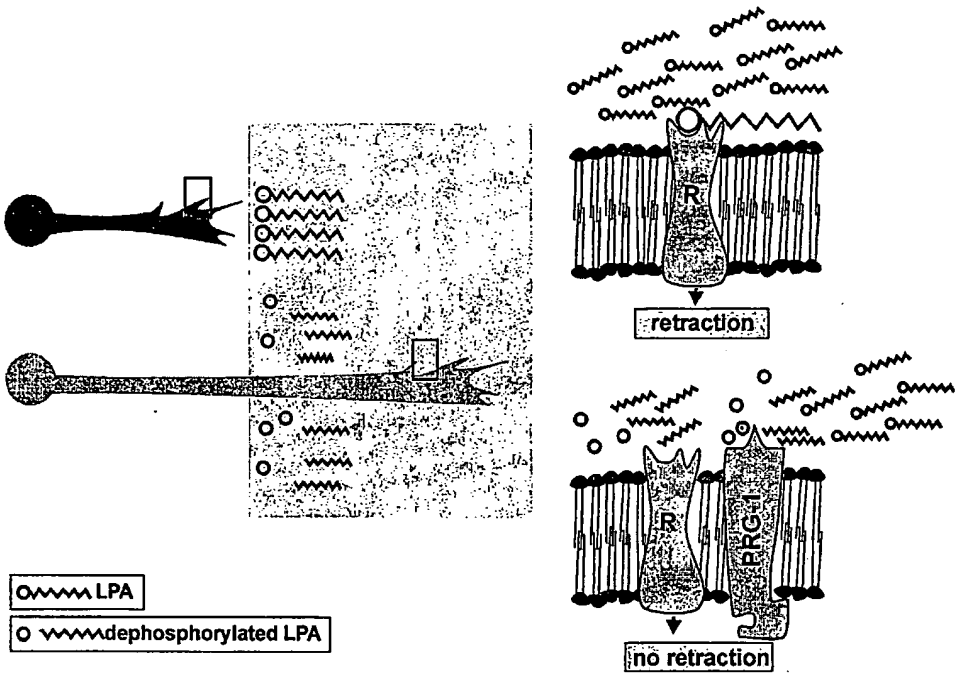

R
retraction
R
RRG-1
no retraction
LPA
dephosphorylated LPA

Figure 14

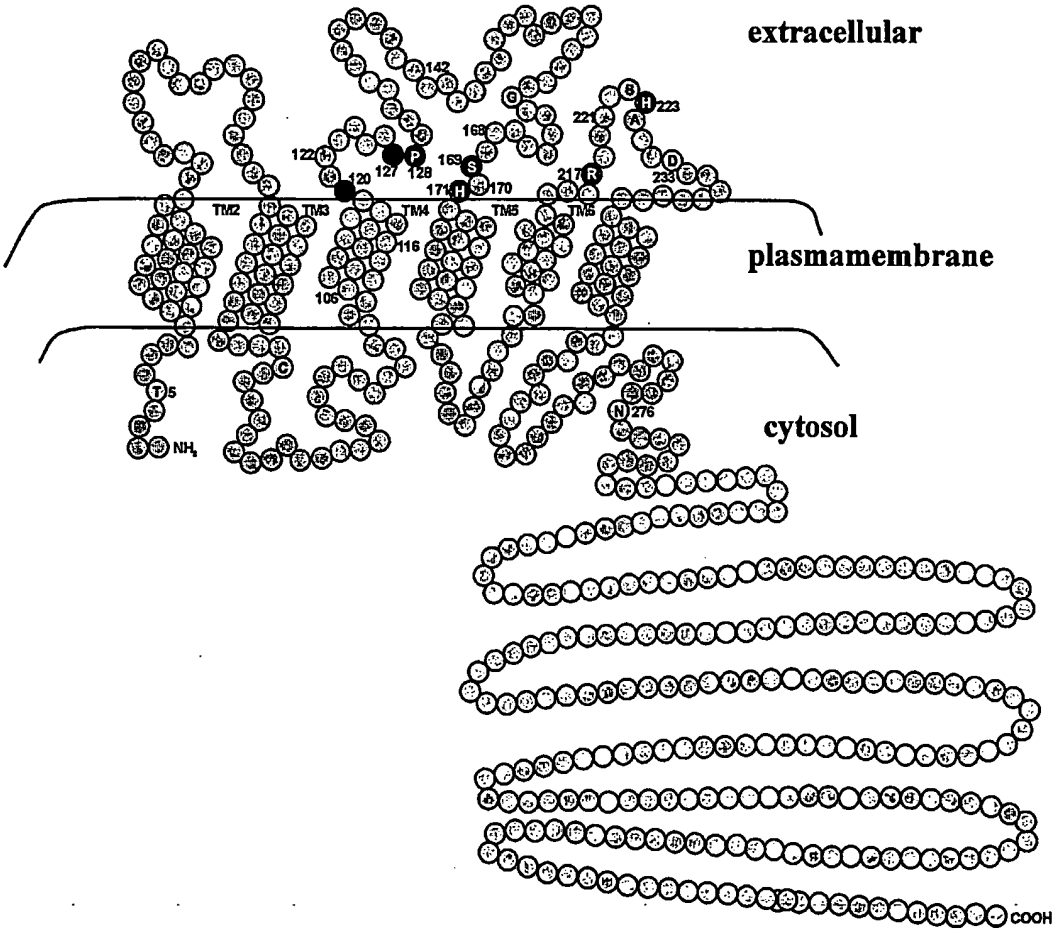

extracellular
plasmamembrane
cytosol
TM2
TM3
TM4
TM5
TM6
142
122
120
127
128
169
168
171
170
217
221
223
233
116
105
T5
NH2
N276
COOH

Figure 15

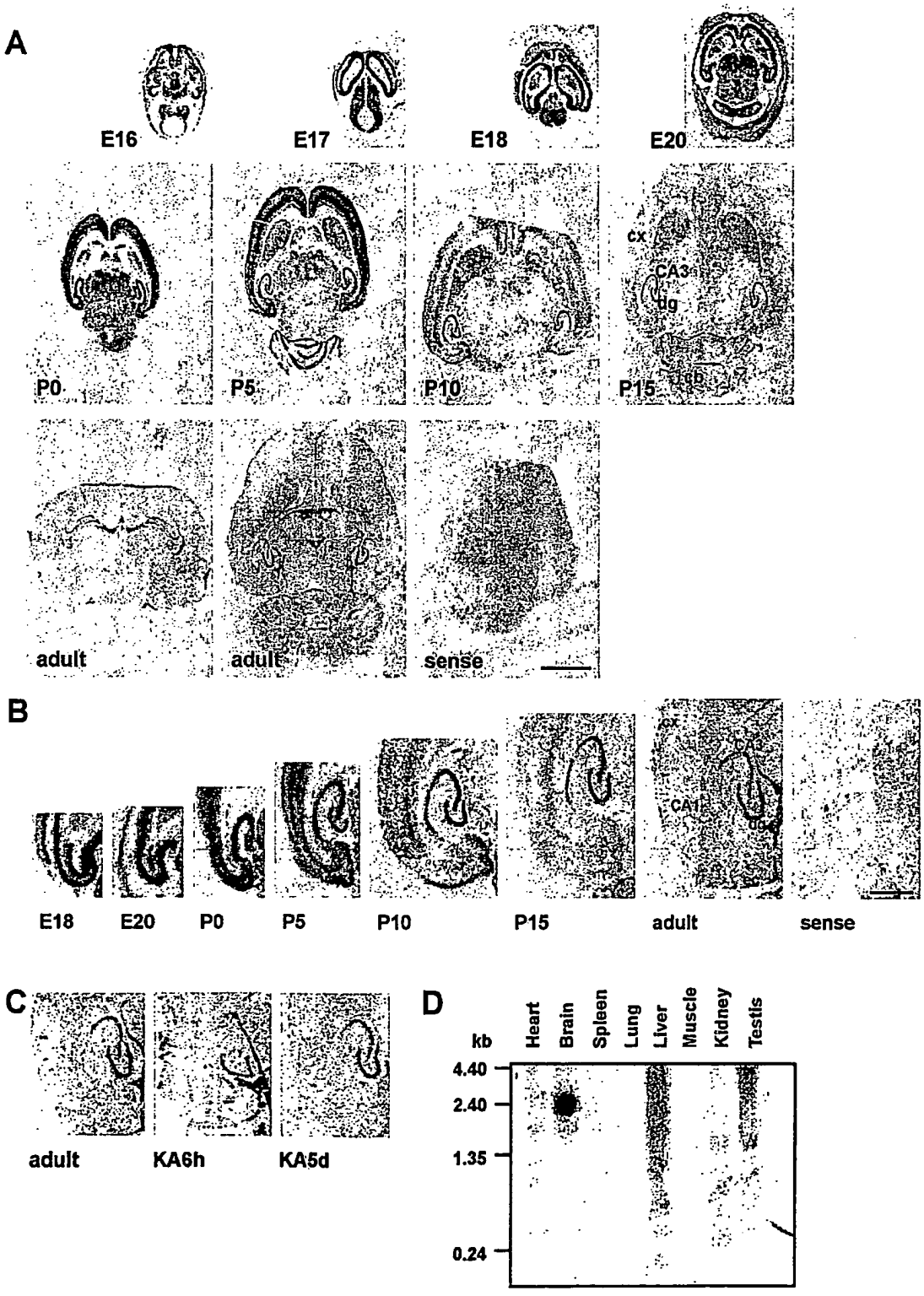
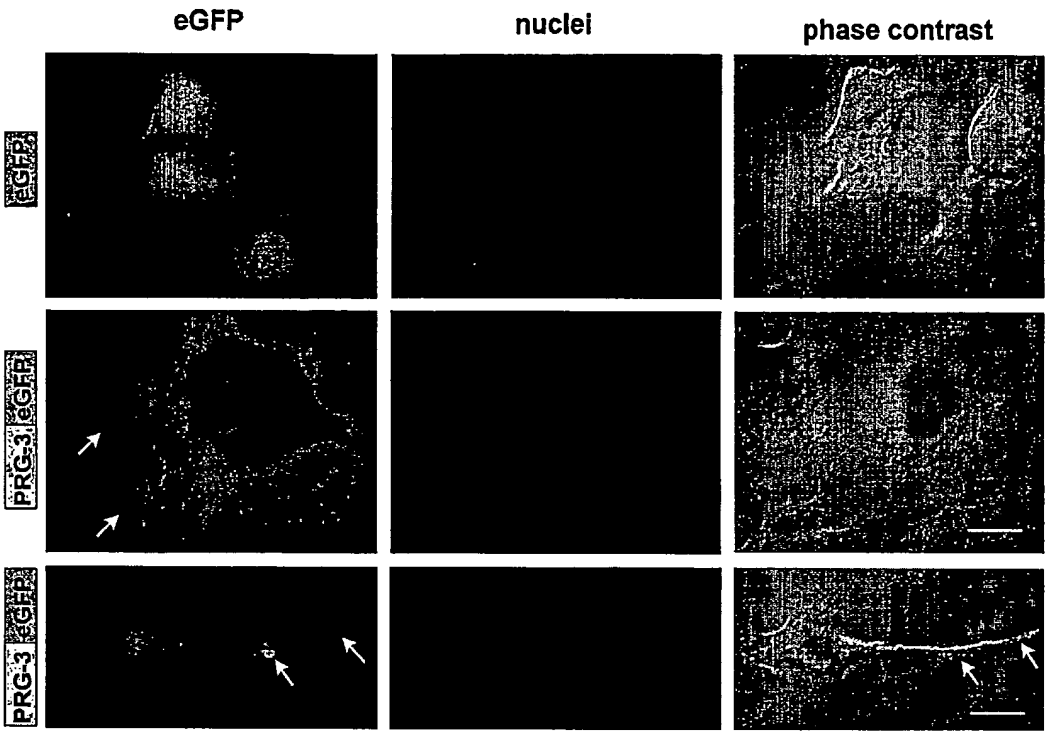

A
E16
E17
E18
E20
P0
P5
P10
P15
cx
CA3
dg
adult
adult
sense
B
E18
E20
P0
P5
P10
P15
adult
sense
CA1
C
adult
KA6h
KA5d
D
kb
Heart
Brain
Spleen
Lung
Liver
Muscle
Kidney
Testis
4.40
2.40
1.35
0.24

Figure 16



SEQUENCE LISTING

<110> Universitätsklinikum Charité an der Humbold-Universität zu Berlin

<120> Lipid phosphate phosphatases and uses thereof for treating neuronal diseases

<130> U30058PCT

<150> EP 02 020 679.3
<151> 2002-09-13

<150> EP 03 002 993.9
<151> 2003-02-11

<160> 38

<170> PatentIn version 3.2

<210> 1
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Met Gln Arg Ala Gly Ser Ser Gly Gly Arg Gly Glu Cys Asp Ile Ser
1 5 10 15

Gly Ala Gly Arg Leu Gly Leu Glu Glu Ala Ala Arg Leu Ser Cys Ala
20 25 30

Val His Thr Ser Pro Gly Gly Gly Arg Arg Pro Gly Gln Ala Ala Gly
35 40 45

Met Ser Ala Lys Glu Arg Pro Lys Gly Lys Val Ile Lys Asp Ser Val
50 55 60

Thr Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Leu Ala Ser
65 70 75 80

Ser Val Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Val Phe Lys Pro
85 90 95

Val His Ser Gly Phe Ser Cys Tyr Asp Arg Ser Leu Ser Met Pro Tyr
100 105 110

Ile Glu Pro Thr Gln Glu Ala Ile Pro Phe Leu Met Leu Leu Ser Leu
115 120 125

Ala Phe Ala Gly Pro Ala Ile Thr Ile Met Val Gly Glu Gly Ile Leu
130 135 140

Tyr Cys Cys Leu Ser Lys Arg Arg Asn Gly Val Gly Leu Glu Pro Asn

```
145                 150                 155                 160

Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg Arg Ala Val
                165                 170                 175

Arg Phe Val Gly Val His Val Phe Gly Leu Cys Ser Thr Ala Leu Ile
            180                 185                 190

Thr Asp Ile Ile Gln Leu Ser Thr Gly Tyr Gln Ala Pro Tyr Phe Leu
        195                 200                 205

Thr Val Cys Lys Pro Asn Tyr Thr Ser Leu Asn Val Ser Cys Lys Glu
    210                 215                 220

Asn Ser Tyr Ile Val Glu Asp Ile Cys Ser Gly Ser Asp Leu Thr Val
225                 230                 235                 240

Ile Asn Ser Gly Arg Lys Ser Phe Pro Ser Gln His Ala Thr Leu Ala
                245                 250                 255

Ala Phe Ala Ala Val Tyr Val Ser Met Tyr Phe Asn Ser Thr Leu Thr
            260                 265                 270

Asp Ser Ser Lys Leu Leu Lys Pro Leu Leu Val Phe Thr Phe Ile Ile
        275                 280                 285

Cys Gly Ile Ile Cys Gly Leu Thr Arg Ile Thr Gln Tyr Lys Asn His
    290                 295                 300

Pro Val Asp Val Tyr Cys Gly Phe Leu Ile Gly Gly Gly Ile Ala Leu
305                 310                 315                 320

Tyr Leu Gly Leu Tyr Ala Val Gly Asn Phe Leu Pro Ser Asp Glu Ser
                325                 330                 335

Met Phe Gln His Arg Asp Ala Leu Arg Ser Leu Thr Asp Leu Asn Gln
            340                 345                 350

Asp Pro Asn Arg Leu Leu Ser Ala Lys Asn Gly Ser Ser Ser Asp Gly
        355                 360                 365

Ile Ala His Thr Glu Gly Ile Leu Asn Arg Asn His Arg Asp Ala Ser
    370                 375                 380

Ser Leu Thr Asn Leu Lys Arg Ala Asn Ala Asp Val Glu Ile Ile Thr
385                 390                 395                 400
```

```
Pro Arg Ser Pro Met Gly Lys Glu Asn Met Val Thr Phe Ser Asn Thr
                405                 410                 415

Leu Pro Arg Ala Asn Thr Pro Ser Val Glu Asp Pro Val Arg Arg Asn
            420                 425                 430

Ala Ser Ile His Ala Ser Met Asp Ser Ala Arg Ser Lys Gln Leu Leu
        435                 440                 445

Thr Gln Trp Lys Asn Lys Asn Glu Ser Arg Lys Leu Ser Leu Gln Val
    450                 455                 460

Ile Glu Pro Glu Pro Gly Gln Ser Pro Pro Arg Ser Ile Glu Met Arg
465                 470                 475                 480

Ser Ser Ser Glu Pro Ser Arg Val Gly Val Asn Gly Asp His His Gly
                485                 490                 495

Pro Gly Asn Gln Tyr Leu Lys Ile Gln Pro Gly Ala Val Pro Gly Cys
            500                 505                 510

Asn Asn Ser Met Pro Gly Gly Pro Arg Val Ser Ile Gln Ser Arg Pro
        515                 520                 525

Gly Ser Ser Gln Leu Val His Ile Pro Glu Glu Thr Gln Glu Asn Ile
    530                 535                 540

Ser Thr Ser Pro Lys Ser Ser Ser Ala Arg Ala Lys Trp Leu Lys Ala
545                 550                 555                 560

Ala Glu Lys Thr Val Ala Cys Asn Arg Ser Asn Ser Gln Pro Arg Ile
                565                 570                 575

Met Gln Val Ile Ala Met Ser Lys Gln Gln Gly Val Leu Gln Ser Ser
            580                 585                 590

Pro Lys Asn Thr Glu Gly Ser Thr Val Ser Cys Thr Gly Ser Ile Arg
        595                 600                 605

Tyr Lys Thr Leu Thr Asp His Glu Pro Ser Gly Ile Val Arg Val Glu
    610                 615                 620

Ala His Pro Glu Asn Asn Arg Pro Ile Ile Gln Ile Pro Ser Thr Glu
625                 630                 635                 640

Gly Glu Gly Ser Gly Ser Trp Lys Trp Lys Ala Pro Glu Lys Gly Ser
                645                 650                 655
```

```
Leu Arg Gln Thr Tyr Glu Leu Asn Asp Leu Asn Arg Asp Ser Glu Ser
            660                 665                 670

Cys Glu Ser Leu Lys Asp Ser Phe Gly Ser Gly Asp Arg Lys Arg Ser
        675                 680                 685

Asn Ile Asp Ser Asn Glu His His His His Gly Ile Thr Thr Ile Arg
    690                 695                 700

Val Thr Pro Val Glu Gly Ser Glu Ile Gly Ser Glu Thr Leu Ser Ile
705                 710                 715                 720

Ser Ser Ser Arg Asp Ser Thr Leu Arg Arg Lys Gly Asn Ile Ile Leu
                725                 730                 735

Ile Pro Glu Arg Ser Asn Ser Pro Glu Asn Thr Arg Asn Ile Phe Tyr
            740                 745                 750

Lys Gly Thr Ser Pro Thr Arg Ala Tyr Lys Asp
        755                 760
```

<210> 2
<211> 746
<212> PRT
<213> Homo sapiens

<400> 2

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Met Ile Ser Thr Lys Glu Lys Asn Lys Ile Pro Lys Asp Ser Met Thr
1               5                   10                  15

Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Val Ala Ser Ser
            20                  25                  30

Ile Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Leu Phe Lys Pro Ala
        35                  40                  45

Lys Val Gly Phe Gln Cys Tyr Asp Arg Thr Leu Ser Met Pro Tyr Val
    50                  55                  60

Glu Thr Asn Glu Glu Leu Ile Pro Leu Leu Met Leu Leu Ser Leu Ala
65                  70                  75                  80

Phe Ala Ala Pro Ala Ala Ser Ile Met Val Ala Glu Gly Met Leu Tyr
                85                  90                  95

Cys Leu Gln Ser Arg Leu Trp Gly Arg Ala Gly Gly Pro Ala Gly Ala
            100                 105                 110
```

```
Glu Gly Ser Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg
        115                 120                 125

Arg Thr Val Arg Phe Val Gly Val His Val Phe Gly Leu Cys Ala Thr
    130                 135                 140

Ala Leu Val Thr Asp Val Ile Gln Leu Ala Thr Gly Tyr His Thr Pro
145                 150                 155                 160

Phe Phe Leu Thr Val Cys Lys Pro Asn Tyr Thr Leu Leu Gly Thr Ser
                165                 170                 175

Cys Glu Val Asn Pro Tyr Ile Thr Gln Asp Ile Cys Ser Gly His Asp
            180                 185                 190

Ile His Ala Ile Leu Ser Ala Arg Lys Thr Phe Pro Ser Gln His Ala
        195                 200                 205

Thr Leu Ser Ala Phe Ala Ala Val Tyr Val Ser Val Ser Pro Ala Pro
    210                 215                 220

His Cys Pro Ser Gln Ala Leu Leu Leu Thr Arg Gly Glu Pro Ser Leu
225                 230                 235                 240

Thr Pro Thr Pro Met Pro Gln Met Tyr Phe Asn Ser Val Ile Ser Asp
                245                 250                 255

Thr Thr Lys Leu Leu Lys Pro Ile Leu Val Phe Ala Phe Ala Ile Ala
            260                 265                 270

Ala Gly Val Cys Gly Leu Thr Gln Ile Thr Gln Tyr Arg Ser His Pro
        275                 280                 285

Val Asp Val Tyr Ala Gly Phe Leu Ile Gly Ala Gly Ile Ala Ala Tyr
    290                 295                 300

Leu Ala Cys His Ala Val Gly Asn Phe Gln Ala Pro Pro Ala Glu Lys
305                 310                 315                 320

Pro Ala Ala Pro Ala Pro Ala Lys Asp Ala Leu Arg Ala Leu Thr Gln
                325                 330                 335

Arg Gly His Asp Ser Val Tyr Gln Gln Asn Lys Ser Val Ser Thr Asp
            340                 345                 350

Glu Leu Gly Pro Pro Gly Arg Leu Glu Gly Ala Pro Arg Pro Val Ala
        355                 360                 365
```

```
Arg Glu Lys Thr Ser Leu Gly Ser Leu Lys Arg Ala Ser Val Asp Val
    370                 375                 380

Asp Leu Leu Ala Pro Arg Ser Pro Met Ala Lys Glu Asn Met Val Thr
385                 390                 395                 400

Phe Ser His Thr Leu Pro Arg Ala Ser Ala Pro Ser Leu Asp Asp Pro
            405                 410                 415

Ala Arg Arg His Met Thr Ile His Val Pro Leu Asp Ala Ser Arg Ser
        420                 425                 430

Lys Gln Leu Ile Ser Glu Trp Lys Gln Lys Ser Leu Glu Gly Arg Gly
    435                 440                 445

Leu Gly Leu Pro Asp Asp Ala Ser Pro Gly His Leu Arg Ala Pro Ala
450                 455                 460

Glu Pro Met Ala Glu Glu Glu Glu Glu Glu Glu Asp Glu Glu Glu Glu
465                 470                 475                 480

Glu Glu Glu Glu Glu Glu Glu Asp Glu Gly Pro Ala Pro Pro Ser Leu
            485                 490                 495

Tyr Pro Thr Val Gln Ala Arg Pro Gly Leu Gly Pro Arg Val Ile Leu
        500                 505                 510

Pro Pro Arg Ala Gly Pro Pro Pro Leu Val His Ile Pro Glu Glu Gly
    515                 520                 525

Ala Gln Thr Gly Ala Gly Leu Ser Pro Lys Ser Gly Ala Gly Val Arg
530                 535                 540

Ala Lys Trp Leu Met Met Ala Glu Lys Ser Gly Ala Ala Val Ala Asn
545                 550                 555                 560

Pro Pro Arg Leu Leu Gln Val Ile Ala Met Ser Lys Ala Pro Gly Ala
            565                 570                 575

Pro Gly Pro Lys Ala Ala Glu Thr Ala Ser Ser Ser Ser Ala Ser Ser
        580                 585                 590

Asp Ser Ser Gln Tyr Arg Ser Pro Ser Asp Arg Asp Ser Ala Ser Ile
    595                 600                 605

Val Thr Ile Asp Ala His Ala Pro His His Pro Val Val His Leu Ser
```

610 615 620

Ala Gly Gly Ala Pro Trp Glu Trp Lys Ala Ala Gly Gly Gly Ala Lys
625 630 635 640

Ala Glu Ala Asp Gly Gly Tyr Glu Leu Gly Asp Leu Ala Arg Gly Phe
645 650 655

Arg Gly Gly Ala Lys Pro Pro Gly Val Ser Pro Gly Ser Ser Val Ser
660 665 670

Asp Val Asp Gln Glu Glu Pro Arg Phe Gly Ala Val Ala Thr Val Asn
675 680 685

Leu Ala Thr Gly Glu Gly Leu Pro Pro Leu Gly Ala Ala Asp Gly Ala
690 695 700

Leu Gly Pro Gly Ser Arg Glu Ser Thr Leu Arg Arg His Ala Gly Gly
705 710 715 720

Leu Gly Leu Ala Glu Arg Glu Ala Glu Ala Glu Ala Glu Gly Tyr Phe
725 730 735

Arg Lys Met Gln Ala Arg Arg Phe Pro Asp
740 745

<210> 3
<211> 325
<212> PRT
<213> Homo sapiens

<400> 3

Met Ala Val Gly Asn Asn Thr Gln Arg Ser Tyr Ser Ile Ile Pro Cys
1 5 10 15

Phe Ile Phe Val Glu Leu Val Ile Met Ala Gly Thr Val Leu Leu Ala
20 25 30

Tyr Tyr Phe Glu Cys Thr Asp Thr Phe Gln Val His Ile Gln Gly Phe
35 40 45

Phe Cys Gln Asp Gly Asp Leu Met Lys Pro Tyr Pro Gly Thr Glu Glu
50 55 60

Glu Ser Phe Ile Thr Pro Leu Val Leu Tyr Cys Val Leu Ala Ala Thr
65 70 75 80

Pro Thr Ala Ile Ile Phe Ile Gly Glu Ile Ser Met Tyr Phe Ile Lys

```
                85                  90                  95

Ser Thr Arg Glu Ser Leu Ile Ala Gln Glu Lys Thr Ile Leu Thr Gly
            100                 105                 110

Glu Cys Cys Tyr Leu Asn Pro Leu Leu Arg Arg Ile Ile Arg Phe Thr
        115                 120                 125

Gly Val Phe Ala Phe Gly Leu Phe Ala Thr Asp Ile Phe Val Asn Ala
    130                 135                 140

Gly Gln Val Val Thr Gly His Leu Thr Pro Tyr Phe Leu Thr Val Cys
145                 150                 155                 160

Lys Pro Asn Tyr Thr Ser Ala Asp Cys Gln Ala His His Gln Phe Ile
                165                 170                 175

Asn Asn Gly Asn Ile Cys Thr Gly Asp Leu Glu Val Ile Glu Lys Ala
            180                 185                 190

Arg Arg Ser Phe Pro Ser Lys His Ala Ala Leu Ser Ile Tyr Ser Ala
        195                 200                 205

Leu Tyr Ala Thr Met Tyr Ile Thr Ser Thr Ile Lys Thr Lys Ser Ser
    210                 215                 220

Arg Leu Ala Lys Pro Val Leu Cys Leu Gly Thr Leu Cys Thr Ala Phe
225                 230                 235                 240

Leu Thr Gly Leu Asn Arg Val Ser Glu Tyr Arg Asn His Cys Ser Asp
                245                 250                 255

Val Ile Ala Gly Phe Ile Leu Gly Thr Ala Val Ala Leu Phe Leu Gly
            260                 265                 270

Met Cys Val Val His Asn Phe Lys Gly Thr Gln Gly Ser Pro Ser Lys
        275                 280                 285

Pro Lys Pro Glu Asp Pro Arg Gly Val Pro Leu Met Ala Phe Pro Arg
    290                 295                 300

Ile Glu Ser Pro Leu Glu Thr Leu Ser Ala Gln Asn His Ser Ala Ser
305                 310                 315                 320

Met Thr Glu Val Thr
                325
```

<210> 4
<211> 343
<212> PRT
<213> Homo sapiens

<400> 4

Met Ala Gly Gly Arg Pro His Leu Lys Arg Ser Phe Ser Ile Ile Pro
1 5 10 15

Cys Phe Val Phe Val Glu Ser Val Leu Leu Gly Ile Val Ile Leu Leu
20 25 30

Ala Tyr Arg Leu Glu Phe Thr Asp Thr Phe Pro Val His Thr Gln Gly
35 40 45

Phe Phe Cys Tyr Asp Ser Thr Tyr Ala Lys Pro Tyr Pro Gly Pro Glu
50 55 60

Ala Ala Ser Arg Val Pro Pro Ala Leu Val Tyr Ala Leu Val Thr Ala
65 70 75 80

Gly Pro Thr Leu Thr Ile Leu Leu Gly Glu Leu Ala Arg Ala Phe Phe
85 90 95

Pro Ala Pro Pro Ser Ala Val Pro Val Ile Gly Glu Ser Thr Ile Val
100 105 110

Ser Gly Ala Cys Cys Arg Phe Ser Pro Pro Val Arg Arg Leu Val Arg
115 120 125

Phe Leu Gly Val Tyr Ser Phe Gly Leu Phe Thr Thr Thr Ile Phe Ala
130 135 140

Asn Ala Gly Gln Val Val Thr Gly Asn Pro Thr Pro His Phe Leu Ser
145 150 155 160

Val Cys Arg Pro Asn Tyr Thr Ala Leu Gly Cys Leu Pro Pro Ser Pro
165 170 175

Asp Arg Pro Gly Pro Asp Arg Phe Val Thr Asp Gln Gly Ala Cys Ala
180 185 190

Gly Ser Pro Ser Leu Val Ala Ala Ala Arg Arg Ala Phe Pro Cys Lys
195 200 205

Asp Ala Ala Leu Cys Ala Tyr Ala Val Thr Tyr Thr Ala Met Tyr Val
210 215 220

```
Thr Leu Val Phe Arg Val Lys Gly Ser Arg Leu Val Lys Pro Ser Leu
225                 230                 235                 240

Cys Leu Ala Leu Leu Cys Pro Ala Phe Leu Val Gly Val Val Arg Val
                245                 250                 255

Ala Glu Tyr Arg Asn His Trp Ser Asp Val Leu Ala Gly Phe Leu Thr
            260                 265                 270

Gly Ala Ala Ile Ala Thr Phe Leu Val Thr Cys Val Val His Asn Phe
        275                 280                 285

Gln Ser Arg Pro Pro Ser Gly Arg Arg Leu Ser Pro Trp Glu Asp Leu
    290                 295                 300

Gly Gln Ala Pro Thr Met Asp Ser Pro Leu Glu Lys Asn Pro Arg Ser
305                 310                 315                 320

Ala Gly Arg Ile Arg His Arg His Gly Ser Pro His Pro Ser Arg Arg
                325                 330                 335

Thr Ala Pro Ala Val Ala Thr
            340
```

<210> 5
<211> 766
<212> PRT
<213> Mus musculus

<400> 5

```
Met Gln Arg Ala Gly Ser Ser Gly Ala Arg Gly Glu Cys Asp Ile Ser
1               5                   10                  15

Gly Ala Gly Arg Leu Arg Leu Glu Gln Ala Ala Arg Leu Gly Gly Arg
            20                  25                  30

Thr Val His Thr Ser Pro Gly Gly Gly Leu Gly Ala Arg Gln Ala Ala
        35                  40                  45

Gly Met Ser Ala Lys Glu Arg Pro Lys Gly Lys Val Ile Lys Asp Ser
    50                  55                  60

Val Thr Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Leu Ala
65                  70                  75                  80

Ser Ser Val Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Val Phe Lys
                85                  90                  95
```

```
Pro Val His Ser Gly Phe Ser Cys Tyr Asp Arg Ser Leu Ser Met Pro
            100                 105                 110

Tyr Ile Glu Pro Thr Gln Glu Ala Ile Pro Phe Leu Met Leu Leu Ser
        115                 120                 125

Leu Ala Phe Ala Gly Pro Ala Ile Thr Ile Met Val Gly Glu Gly Ile
    130                 135                 140

Leu Tyr Cys Cys Leu Ser Lys Arg Arg Asn Gly Ala Gly Leu Glu Pro
145                 150                 155                 160

Asn Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg Arg Ala
                165                 170                 175

Val Arg Phe Val Gly Val His Val Phe Gly Leu Cys Ser Thr Ala Leu
            180                 185                 190

Ile Thr Asp Ile Ile Gln Leu Ser Thr Gly Tyr Gln Ala Pro Tyr Phe
        195                 200                 205

Leu Thr Val Cys Lys Pro Asn Tyr Thr Ser Leu Asn Val Ser Cys Lys
    210                 215                 220

Glu Asn Ser Tyr Ile Val Glu Asp Ile Cys Ser Gly Ser Asp Leu Thr
225                 230                 235                 240

Val Ile Asn Ser Gly Arg Lys Ser Phe Pro Ser Gln His Ala Thr Leu
                245                 250                 255

Ala Ala Phe Ala Ala Val Tyr Val Ser Met Tyr Phe Asn Ser Thr Leu
            260                 265                 270

Thr Asp Ser Ser Lys Leu Leu Lys Pro Leu Leu Val Phe Thr Phe Ile
        275                 280                 285

Ile Cys Gly Ile Ile Cys Gly Leu Thr Arg Ile Thr Gln Tyr Lys Asn
    290                 295                 300

His Pro Val Asp Val Tyr Cys Gly Phe Leu Ile Gly Gly Gly Ile Ala
305                 310                 315                 320

Leu Tyr Leu Gly Leu Tyr Ala Val Gly Asn Phe Leu Pro Ser Glu Asp
                325                 330                 335

Ser Met Leu Gln His Arg Asp Ala Leu Arg Ser Leu Thr Asp Leu Asn
            340                 345                 350
```

```
Gln Asp Pro Ser Arg Val Leu Ser Ala Lys Asn Gly Ser Ser Gly Asp
        355                 360                 365

Gly Ile Ala His Thr Glu Gly Ile Leu Asn Arg Asn His Arg Asp Ala
    370                 375                 380

Ser Ser Leu Thr Asn Leu Lys Arg Ala Asn Ala Asp Val Glu Ile Ile
385                 390                 395                 400

Thr Pro Arg Ser Pro Met Gly Lys Glu Ser Met Val Thr Phe Ser Asn
                405                 410                 415

Thr Leu Pro Arg Ala Asn Thr Pro Ser Val Glu Asp Pro Val Arg Arg
            420                 425                 430

Asn Ala Ser Ile His Ala Ser Met Asp Ser Ala Arg Ser Lys Gln Leu
        435                 440                 445

Leu Thr Gln Trp Lys Ser Lys Asn Glu Ser Arg Lys Met Ser Leu Gln
    450                 455                 460

Val Met Asp Thr Glu Pro Glu Gly Gln Ser Pro Pro Arg Ser Ile Glu
465                 470                 475                 480

Met Arg Ser Ser Ser Glu Pro Ser Arg Val Gly Val Asn Gly Asp His
                485                 490                 495

His Val Pro Gly Asn Gln Tyr Leu Lys Ile Gln Pro Gly Thr Val Pro
            500                 505                 510

Gly Cys Asn Asn Ser Met Pro Gly Gly Pro Arg Val Ser Ile Gln Ser
        515                 520                 525

Arg Pro Gly Ser Ser Gln Leu Val His Ile Pro Glu Glu Thr Gln Glu
    530                 535                 540

Asn Ile Ser Thr Ser Pro Lys Ser Ser Ser Ala Arg Ala Lys Trp Leu
545                 550                 555                 560

Lys Ala Ala Glu Lys Thr Val Asp Cys Asn Arg Ser Asn Asn Gln Pro
                565                 570                 575

Arg Ile Met Gln Val Ile Ala Met Ser Lys Gln Gln Gly Val Leu Gln
            580                 585                 590

Ser Ser Pro Lys Asn Ala Glu Gly Ser Thr Val Thr Cys Thr Gly Ser
        595                 600                 605
```

```
Ile Arg Tyr Lys Thr Leu Thr Asp His Glu Pro Ser Gly Ile Val Arg
    610                 615                 620

Val Glu Ala His Pro Glu Asn Asn Arg Pro Ile Ile Gln Ile Pro Ser
625                 630                 635                 640

Ser Thr Glu Gly Glu Gly Ser Gly Ser Trp Lys Trp Lys Val Pro Glu
                645                 650                 655

Lys Ser Ser Leu Arg Gln Thr Tyr Glu Leu Asn Asp Leu Asn Arg Asp
            660                 665                 670

Ser Glu Ser Cys Glu Ser Leu Lys Asp Ser Phe Gly Ser Gly Asp Arg
        675                 680                 685

Lys Arg Ser Asn Ile Asp Ser Asn Glu His His His His Gly Ile Thr
    690                 695                 700

Thr Ile Arg Val Thr Pro Val Glu Gly Ser Glu Ile Gly Ser Glu Thr
705                 710                 715                 720

Leu Ser Val Ser Ser Ser Arg Asp Ser Thr Leu Arg Arg Lys Gly Asn
                725                 730                 735

Ile Ile Leu Ile Pro Glu Arg Ser Asn Ser Pro Glu Asn Thr Arg Asn
            740                 745                 750

Ile Phe Tyr Lys Gly Thr Ser Pro Thr Arg Ala Tyr Lys Asp
        755                 760                 765
```

<210> 6
<211> 716
<212> PRT
<213> Mus musculus

<400> 6

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Met Leu Ala Met Lys Glu Lys Asn Lys Thr Pro Lys Asp Ser Met Thr
1               5                   10                  15

Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Val Ala Ser Ser
            20                  25                  30

Ile Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Leu Phe Lys Pro Ala
        35                  40                  45

Lys Val Gly Phe Gln Cys Tyr Asp Arg Ala Leu Ser Met Pro Tyr Val
    50                  55                  60
```

```
Glu Thr Asn Glu Glu Leu Ile Pro Leu Leu Met Leu Leu Ser Leu Ala
65                  70                  75                  80

Phe Ala Ala Pro Ala Ala Ser Ile Met Val Gly Glu Gly Met Val Tyr
                85                  90                  95

Cys Leu Gln Ser Arg Leu Trp Gly Arg Gly Pro Gly Gly Val Glu Gly
            100                 105                 110

Ser Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg Arg Thr
        115                 120                 125

Val Arg Phe Val Gly Val His Val Phe Gly Leu Cys Ala Thr Ala Leu
    130                 135                 140

Val Thr Asp Val Ile Gln Leu Ala Thr Gly Tyr His Thr Pro Phe Phe
145                 150                 155                 160

Leu Thr Val Cys Lys Pro Asn Tyr Thr Leu Leu Gly Thr Ser Cys Glu
                165                 170                 175

Ser Asn Pro Tyr Ile Thr Gln Asp Ile Cys Ser Gly His Asp Thr His
            180                 185                 190

Ala Ile Leu Ser Ala Arg Lys Thr Phe Pro Ser Gln His Ala Thr Leu
        195                 200                 205

Ser Ala Phe Ala Ala Val Tyr Val Ser Met Tyr Phe Asn Ala Val Ile
    210                 215                 220

Ser Asp Thr Thr Lys Leu Leu Lys Pro Ile Leu Val Phe Ala Phe Ala
225                 230                 235                 240

Ile Ala Ala Gly Val Cys Gly Leu Thr Gln Ile Thr Gln Tyr Arg Ser
                245                 250                 255

His Pro Val Asp Val Tyr Ala Gly Phe Leu Ile Gly Ala Gly Ile Ala
            260                 265                 270

Ala Tyr Leu Ala Cys His Ala Val Gly Asn Phe Gln Ala Pro Pro Ala
        275                 280                 285

Glu Lys Val Pro Thr Pro Ala Pro Ala Lys Asp Ala Leu Arg Ala Leu
    290                 295                 300

Thr Gln Arg Gly His Glu Ser Met Tyr Gln Gln Asn Lys Ser Val Ser
```

305 310 315 320

Thr Asp Glu Leu Gly Pro Pro Gly Arg Leu Glu Gly Val Pro Arg Pro
325 330 335

Val Ala Arg Glu Lys Thr Ser Leu Gly Ser Leu Lys Arg Ala Ser Val
340 345 350

Asp Val Asp Leu Leu Ala Pro Arg Ser Pro Met Gly Lys Glu Gly Met
355 360 365

Val Thr Phe Ser Asn Thr Leu Pro Arg Val Ser Thr Pro Ser Leu Asp
370 375 380

Asp Pro Ala Arg Arg His Met Thr Ile His Val Pro Leu Asp Ala Ser
385 390 395 400

Arg Ser Arg Gln Leu Ile Gly Glu Trp Lys Gln Lys Ser Leu Glu Gly
405 410 415

Arg Gly Leu Gly Leu Pro Asp Glu Ala Ser Pro Val His Leu Arg Ala
420 425 430

Pro Ala Glu Gln Val Ala Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
435 440 445

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Pro Val Pro Pro Ser
450 455 460

Leu Tyr Pro Thr Val Gln Ala Arg Pro Gly Leu Gly Pro Arg Val Ile
465 470 475 480

Leu Pro Pro Arg Pro Gly Pro Gln Pro Leu Val His Ile Pro Glu Glu
485 490 495

Gly Val Gln Ala Gly Ala Gly Leu Ser Pro Lys Ser Ser Ser Ser Ser
500 505 510

Val Arg Ala Lys Trp Leu Ser Val Ala Glu Lys Gly Gly Gly Pro Val
515 520 525

Ala Val Ala Pro Ser Gln Pro Arg Val Ala Asn Pro Pro Arg Leu Leu
530 535 540

Gln Val Ile Ala Met Ser Lys Ala Ala Gly Gly Pro Lys Ala Glu Thr
545 550 555 560

```
Ala Ser Ser Ser Ser Ala Ser Ser Asp Ser Ser Gln Tyr Arg Ser Pro
                565                 570                 575

Ser Asp Arg Asp Ser Ala Ser Ile Val Thr Ile Asp Ala His Ala Pro
            580                 585                 590

His His Pro Val Val His Leu Ser Ala Gly Ser Thr Pro Trp Glu Trp
        595                 600                 605

Lys Ala Lys Val Val Glu Gly Glu Gly Ser Tyr Glu Leu Gly Asp Leu
    610                 615                 620

Ala Arg Gly Phe Arg Ser Ser Cys Lys Gln Pro Gly Met Gly Pro Gly
625                 630                 635                 640

Ser Pro Val Ser Asp Val Asp Gln Glu Glu Pro Arg Phe Gly Ala Val
                645                 650                 655

Ala Thr Val Asn Leu Ala Thr Gly Glu Gly Leu Pro Pro Pro Gly Ala
            660                 665                 670

Ser Glu Gly Ala Leu Gly Ala Gly Ser Arg Glu Ser Thr Leu Arg Arg
        675                 680                 685

Gln Val Gly Gly Leu Ala Glu Arg Glu Val Glu Ala Glu Ala Glu Ser
    690                 695                 700

Tyr Tyr Arg Arg Met Gln Ala Arg Arg Tyr Gln Asp
705                 710                 715
```

<210> 7
<211> 325
<212> PRT
<213> Mus musculus

<400> 7

```
Met Ala Val Glu Asn Asn Thr Gln Arg Ser Tyr Ser Ile Ile Pro Cys
1               5                   10                  15

Phe Ile Phe Val Glu Leu Val Ile Met Ala Gly Thr Val Leu Leu Ala
            20                  25                  30

Tyr Tyr Phe Glu Cys Thr Asp Thr Phe Gln Val His Ile Gln Gly Phe
        35                  40                  45

Phe Cys Gln Asp Gly Asp Leu Met Lys Pro Tyr Pro Gly Thr Glu Glu
    50                  55                  60
```

```
Glu Ser Phe Ile Ser Pro Leu Val Leu Tyr Cys Val Leu Ala Ala Thr
65                  70                  75                  80

Pro Thr Ala Ile Ile Phe Ile Gly Glu Ile Ser Met Tyr Phe Ile Lys
                85                  90                  95

Ser Thr Arg Glu Ser Leu Ile Ala Glu Glu Lys Met Ile Leu Thr Gly
            100                 105                 110

Asp Cys Cys Tyr Leu Ser Pro Leu Leu Arg Arg Ile Ile Arg Phe Ile
        115                 120                 125

Gly Val Phe Ala Phe Gly Leu Phe Ala Thr Asp Ile Phe Val Asn Ala
    130                 135                 140

Gly Gln Val Val Thr Gly His Leu Thr Pro Tyr Phe Leu Thr Val Cys
145                 150                 155                 160

Gln Pro Asn Tyr Thr Ser Thr Asp Cys Arg Ala His Gln Gln Phe Ile
                165                 170                 175

Asn Asn Gly Asn Ile Cys Thr Gly Asp Leu Glu Val Ile Glu Lys Ala
            180                 185                 190

Arg Arg Ser Phe Pro Ser Lys His Ala Ala Leu Ser Ile Tyr Ser Ala
        195                 200                 205

Leu Tyr Ala Thr Met Tyr Ile Thr Ser Thr Ile Lys Thr Lys Ser Ser
    210                 215                 220

Arg Leu Ala Lys Pro Val Leu Cys Leu Gly Thr Leu Cys Thr Ala Phe
225                 230                 235                 240

Leu Thr Gly Leu Asn Arg Val Ser Glu Tyr Arg Asn His Cys Ser Asp
                245                 250                 255

Val Ile Ala Gly Phe Ile Leu Gly Thr Ala Val Ala Leu Phe Leu Gly
            260                 265                 270

Met Cys Val Val His Asn Phe Arg Gly Thr Gln Gly Ser Pro Ser Lys
        275                 280                 285

Pro Lys Pro Glu Asp Pro Arg Gly Val Pro Leu Met Ala Phe Pro Arg
    290                 295                 300

Ile Glu Ser Pro Leu Glu Thr Leu Ser Ala Gln Asn His Ser Ala Ser
305                 310                 315                 320
```

Met Thr Glu Val Thr
325

<210> 8
<211> 343
<212> PRT
<213> Mus musculus

<400> 8

Met Ala Gly Gly Arg Pro His Leu Lys Arg Ser Phe Ser Ile Ile Pro
1 5 10 15

Cys Phe Val Phe Val Glu Ser Val Leu Leu Gly Ile Val Val Leu Leu
20 25 30

Ala Tyr Arg Leu Glu Phe Thr Asp Thr Phe Pro Val His Thr Gln Gly
35 40 45

Phe Phe Cys Tyr Asp Ser Ala Tyr Ala Lys Pro Tyr Pro Gly Pro Glu
50 55 60

Ala Ala Ser Arg Ala Pro Pro Ala Leu Ile Tyr Ala Leu Val Thr Ala
65 70 75 80

Gly Pro Thr Leu Thr Ile Leu Leu Gly Glu Leu Ala Arg Ala Phe Phe
85 90 95

Pro Ala Pro Pro Ser Ser Ser Pro Val Ser Gly Glu Ser Thr Ile Val
100 105 110

Ser Gly Ala Cys Cys Arg Phe Ser Pro Pro Leu Arg Arg Leu Val Arg
115 120 125

Phe Leu Gly Val Tyr Ser Phe Gly Leu Phe Thr Thr Thr Ile Phe Ala
130 135 140

Asn Ala Gly Gln Val Val Thr Gly Asn Pro Thr Pro His Phe Leu Ser
145 150 155 160

Val Cys Arg Pro Asn Tyr Thr Ala Leu Gly Cys Pro Pro Pro Ser Pro
165 170 175

Asp Arg Pro Gly Pro Asp Arg Phe Val Thr Asp Gln Ser Ala Cys Ala
180 185 190

Gly Ser Pro Ser Leu Val Ala Ala Ala Arg Arg Ala Phe Pro Cys Lys
195 200 205

```
Asp Ala Ala Leu Cys Ala Tyr Ala Val Thr Tyr Thr Ala Met Tyr Val
    210                 215                 220

Thr Leu Val Phe Arg Val Lys Gly Ser Arg Leu Val Lys Pro Ser Leu
225                 230                 235                 240

Cys Leu Ala Leu Leu Cys Pro Ala Phe Leu Val Gly Val Val Arg Val
                245                 250                 255

Ala Glu Tyr Arg Asn His Trp Ser Asp Val Leu Ala Gly Phe Leu Thr
            260                 265                 270

Gly Ala Ala Ile Ala Thr Phe Leu Val Thr Cys Val Val His Asn Phe
        275                 280                 285

Gln Ser Arg Pro His Ser Gly Arg Arg Leu Ser Pro Trp Glu Asp Leu
    290                 295                 300

Ser Gln Ala Pro Thr Met Asp Ser Pro Leu Glu Lys Asn Pro Arg Pro
305                 310                 315                 320

Ala Gly Arg Ile Arg His Arg His Gly Ser Pro His Pro Ser Arg Arg
                325                 330                 335

Thr Val Pro Ala Val Ala Thr
            340
```

<210> 9
<211> 766
<212> PRT
<213> Rattus norvegicus

<400> 9

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Met Gln Arg Ala Gly Ser Ser Gly Ala Arg Gly Glu Cys Asp Ile Ser
1               5                   10                  15

Gly Thr Gly Arg Leu Arg Leu Glu Gln Ala Ala Arg Leu Gly Gly Arg
            20                  25                  30

Ala Val His Thr Ser Pro Thr Gly Gly Leu Gly Ala Arg Gln Val Ala
        35                  40                  45

Gly Met Ser Ala Lys Glu Arg Pro Lys Gly Lys Val Ile Lys Asp Ser
    50                  55                  60

Val Thr Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Leu Ala
65                  70                  75                  80
```

```
Ser Ser Val Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Val Phe Lys
                85                  90                  95

Pro Val His Ser Gly Phe Ser Cys Tyr Asp Arg Ser Leu Ser Met Pro
            100                 105                 110

Tyr Ile Glu Pro Thr Gln Glu Ala Ile Pro Phe Leu Met Leu Leu Ser
        115                 120                 125

Leu Ala Phe Ala Gly Pro Ala Ile Thr Ile Met Val Gly Glu Gly Ile
    130                 135                 140

Leu Tyr Cys Cys Leu Ser Lys Arg Arg Asn Gly Ala Gly Leu Glu Pro
145                 150                 155                 160

Asn Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg Arg Ala
                165                 170                 175

Val Arg Phe Val Gly Val His Val Val Gly Leu Cys Ser Thr Ala Leu
            180                 185                 190

Ile Thr Asp Ile Ile Gln Leu Ala Thr Gly Tyr Gln Ala Pro Tyr Phe
        195                 200                 205

Leu Thr Val Cys Lys Pro Met Tyr Thr Ser Leu Glu Gly Ser Cys Lys
    210                 215                 220

Glu Asn Ser Tyr Ile Val Glu Glu Ile Cys Ser Gly Ser Asp Leu Thr
225                 230                 235                 240

Val Ile Asn Asn Gly Lys Lys Ser Phe Pro Ser Gln His Ala Thr Leu
                245                 250                 255

Ala Ala Phe Ala Ala Val Tyr Val Ser Met Tyr Phe Asn Ser Thr Leu
            260                 265                 270

Thr Asp Ser Ser Lys Leu Leu Lys Pro Leu Leu Val Phe Thr Phe Ile
        275                 280                 285

Ile Cys Gly Ile Ile Cys Gly Leu Thr Arg Ile Thr Gln Tyr Lys Asn
    290                 295                 300

His Pro Val Asp Val Tyr Cys Gly Phe Leu Ile Gly Gly Gly Ile Ala
305                 310                 315                 320

Leu Tyr Leu Gly Leu Tyr Ala Val Gly Asn Phe Leu Pro Ser Glu Asp
                325                 330                 335
```

```
Ser Met Leu Gln His Arg Asp Ala Leu Arg Ser Leu Thr Asp Leu Asn
            340                 345                 350

Gln Asp Pro Ser Arg Val Leu Ser Ala Lys Asn Gly Ser Ser Gly Asp
        355                 360                 365

Gly Ile Ala His Thr Glu Gly Ile Leu Asn Arg Asn His Arg Asp Ala
    370                 375                 380

Ser Ser Leu Thr Asn Leu Lys Arg Ala Asn Ala Asp Val Glu Ile Ile
385                 390                 395                 400

Thr Pro Arg Ser Pro Met Gly Lys Glu Ser Met Val Thr Phe Ser Asn
                405                 410                 415

Thr Leu Pro Arg Ala Asn Thr Pro Ser Val Glu Asp Pro Val Arg Arg
            420                 425                 430

Asn Ala Ser Ile His Ala Ser Met Asp Ser Ala Arg Ser Lys Gln Leu
        435                 440                 445

Leu Thr Gln Trp Lys Ser Lys Asn Glu Ser Arg Lys Met Ser Leu Gln
    450                 455                 460

Val Met Asp Ser Glu Pro Glu Gly Gln Ser Pro Pro Arg Ser Ile Glu
465                 470                 475                 480

Met Arg Ser Ser Ser Glu Pro Ser Arg Val Gly Val Asn Gly Asp His
                485                 490                 495

His Val Pro Gly Asn Gln Tyr Leu Lys Ile Gln Pro Gly Thr Val Pro
            500                 505                 510

Gly Cys Asn Asn Ser Met Pro Ala Gly Pro Arg Val Ser Ile Gln Ser
        515                 520                 525

Arg Pro Gly Ser Ser Gln Leu Val His Ile Pro Glu Glu Thr Gln Glu
    530                 535                 540

Asn Ile Ser Thr Ser Pro Lys Ser Ser Ser Ala Arg Ala Lys Trp Leu
545                 550                 555                 560

Lys Ala Ala Glu Lys Thr Val Ala Cys Asn Arg Gly Asn Asn Gln Pro
                565                 570                 575

Arg Ile Met Gln Val Ile Ala Met Ser Lys Gln Gln Gly Val Leu Gln
```

580 585 590

Ser Ser Pro Lys Asn Ala Glu Gly Ser Thr Val Thr Cys Thr Gly Ser
595 600 605

Ile Arg Tyr Lys Thr Leu Thr Asp His Glu Pro Ser Gly Ile Val Arg
610 615 620

Val Glu Ala His Pro Glu Asn Asn Arg Pro Ile Ile Gln Ile Pro Ser
625 630 635 640

Ser Thr Glu Gly Glu Gly Ser Gly Ser Trp Lys Trp Lys Ala Pro Glu
645 650 655

Lys Ser Ser Leu Arg Gln Thr Tyr Glu Leu Asn Asp Leu Asn Arg Asp
660 665 670

Ser Glu Ser Cys Glu Ser Leu Lys Asp Ser Phe Gly Ser Gly Asp Arg
675 680 685

Lys Arg Lys His Ile Asp Ser Asn Glu His His His His Gly Ile Thr
690 695 700

Thr Ile Arg Val Thr Pro Val Glu Gly Ser Glu Ile Gly Ser Glu Thr
705 710 715 720

Leu Ser Val Ser Ser Ser Arg Asp Ser Thr Leu Arg Arg Lys Gly Asn
725 730 735

Ile Ile Leu Ile Pro Glu Arg Ser Asn Ser Pro Glu Asn Thr Arg Asn
740 745 750

Ile Phe Tyr Lys Gly Thr Ser Pro Thr Arg Pro Tyr Lys Asp
755 760 765

<210> 10
<211> 748
<212> PRT
<213> Rattus norvegicus

<400> 10

Met Ile Ala Lys Lys Glu Lys Asn Lys Thr Pro Lys Asp Ser Met Thr
1 5 10 15

Leu Leu Pro Cys Phe Tyr Phe Val Glu Leu Pro Ile Val Ala Ser Ser
20 25 30

Val Val Ser Leu Tyr Phe Leu Glu Leu Thr Asp Leu Phe Gln Pro Ala

```
        35                  40                  45

Lys Val Gly Phe Gln Cys His Asp Arg Ser Leu Ser Met Pro Tyr Val
    50                  55                  60

Glu Thr Asn Glu Glu Leu Ile Pro Leu Leu Met Leu Leu Ser Leu Ala
65                  70                  75                  80

Phe Ala Ala Pro Ala Ala Ser Ile Met Val Gly Glu Gly Met Val Tyr
                85                  90                  95

Cys Leu Gln Ser Arg Leu Trp Gly Arg Gly Pro Gly Gly Val Glu Gly
            100                 105                 110

Ser Ile Asn Ala Gly Gly Cys Asn Phe Asn Ser Phe Leu Arg Arg Thr
        115                 120                 125

Val Arg Phe Val Gly Val His Val Phe Gly Leu Cys Ala Thr Ala Leu
    130                 135                 140

Val Thr Asp Val Ile Gln Leu Ala Thr Gly Tyr His Thr Pro Phe Phe
145                 150                 155                 160

Leu Thr Val Cys Lys Pro Asn Tyr Thr Leu Leu Gly Thr Ser Cys Glu
                165                 170                 175

Ala Asn Pro Tyr Ile Thr Gln Asp Ile Cys Ser Gly His Asp Thr His
            180                 185                 190

Ala Ile Leu Ser Ala Arg Lys Thr Phe Pro Ser Gln His Ala Thr Leu
        195                 200                 205

Ser Ala Phe Ala Ala Val Tyr Val Ser Met Tyr Phe Asn Ser Val Ile
    210                 215                 220

Ser Asp Ala Thr Lys Leu Leu Lys Pro Ile Leu Val Phe Ala Phe Ala
225                 230                 235                 240

Ile Ala Ala Gly Val Cys Gly Leu Thr Gln Ile Thr Gln Tyr Arg Ser
                245                 250                 255

His Pro Val Asp Val Tyr Ala Gly Phe Leu Ile Gly Ala Gly Ile Ala
            260                 265                 270

Ala Tyr Leu Ala Cys His Ala Val Gly Asn Phe Gln Ala Pro Pro Ala
        275                 280                 285
```

```
Glu Lys Val Pro Thr Pro Ala Pro Ala Lys Asp Ala Leu Arg Val Leu
    290                 295                 300

Thr Gln Arg Gly His Glu Ser Met Tyr Gln Gln Asn Lys Ser Val Ser
305                 310                 315                 320

Thr Asp Glu Leu Gly Pro Pro Gly Arg Leu Glu Gly Val Pro Arg Pro
                325                 330                 335

Val Ala Arg Glu Lys Thr Ser Leu Gly Ser Leu Lys Arg Ala Ser Val
            340                 345                 350

Asp Val Asp Leu Leu Ala Pro Arg Ser Pro Met Gly Lys Glu Gly Met
        355                 360                 365

Val Thr Phe Ser Asn Thr Leu Pro Arg Val Ser Thr Pro Ser Leu Asp
    370                 375                 380

Asp Pro Ser Arg Arg His Met Thr Ile His Val Pro Leu Asp Ala Ser
385                 390                 395                 400

Arg Ser Arg Gln Leu Ile Ser Glu Trp Lys Gln Lys Ser Leu Glu Gly
                405                 410                 415

Arg Gly Leu Gly Leu Pro Asp Glu Ala Ser Pro Ala His Leu Arg Ala
            420                 425                 430

Pro Ala Glu Gln Val Ala Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
        435                 440                 445

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Pro Val Pro Pro
    450                 455                 460

Ser Leu Tyr Pro Thr Val Gln Ala Arg Pro Gly Leu Gly Pro Arg Val
465                 470                 475                 480

Ile Leu Pro Pro Arg Pro Gly Pro Gln Pro Leu Ile His Ile Pro Glu
                485                 490                 495

Glu Val Val Gln Ala Gly Ala Gly Leu Ser Pro Lys Ser Ser Ala Ser
            500                 505                 510

Val Arg Ala Lys Trp Leu Ser Met Val Glu Lys Gly Gly Gly Pro Val
        515                 520                 525

Ala Val Ala Pro Pro Gln Pro Arg Val Ala Asn Pro Pro Arg Leu Leu
    530                 535                 540
```

```
Gln Val Ile Ala Met Ser Lys Ala Ala Gly Gly Pro Lys Ala Glu Thr
545                 550                 555                 560

Ala Ser Ser Ser Ser Ala Ser Ser Asp Ser Ser Gln Tyr Arg Ser Pro
                565                 570                 575

Ser Asp Arg Asp Ser Ala Ser Ile Val Thr Ile Asp Ala His Ala Pro
            580                 585                 590

His His Pro Val Val His Leu Ser Ala Gly Ser Thr Pro Trp Glu Trp
        595                 600                 605

Lys Ala Lys Val Val Glu Gly Glu Gly Gly Tyr Glu Leu Gly Asp Leu
    610                 615                 620

Ala Arg Gly Phe Arg Ser Ser Cys Lys Gln Pro Gly Ile Gly Pro Gly
625                 630                 635                 640

Ser Pro Val Ser Asp Val Asp Gln Glu Glu Pro Arg Phe Gly Ala Val
                645                 650                 655

Ala Thr Val Asn Leu Ala Thr Gly Glu Gly Leu Pro Pro Pro Gly Ala
            660                 665                 670

Ser Glu Gly Ala Leu Gly Ala Gly Ser Arg Glu Ser Thr Leu Arg Arg
        675                 680                 685

Gln Val Gly Ala Leu Gly Glu Arg Glu Val Glu Ala Glu Ala Glu Ser
    690                 695                 700

Tyr Tyr Arg Arg Met Gln Ala Arg Arg Tyr Gln Asp Ala Trp Gln Ser
705                 710                 715                 720

Cys Asp Gly Gln Lys Ala Gly Trp Gly Val Thr Thr Ala Pro Pro Ile
                725                 730                 735

Lys Val His Gly Asn Arg Lys Lys Lys Lys Lys Lys
            740                 745

<210>  11
<211>  325
<212>  PRT
<213>  Rattus norvegicus

<400>  11

Met Ala Val Glu Asn Asn Thr Gln Arg Ser Tyr Ser Ile Ile Pro Cys
1               5                   10                  15
```

```
Phe Ile Phe Val Glu Leu Val Ile Met Ala Gly Thr Val Leu Leu Ala
            20                  25                  30

Tyr Tyr Phe Glu Cys Thr Asp Thr Phe Gln Val His Ile Gln Gly Phe
        35                  40                  45

Phe Cys Gln Asp Gly Asp Leu Met Lys Pro Tyr Pro Gly Thr Glu Glu
    50                  55                  60

Glu Ser Phe Ile Ser Pro Leu Val Leu Tyr Cys Val Leu Ala Ala Thr
65                  70                  75                  80

Pro Thr Ala Ile Ile Phe Ile Gly Glu Ile Ser Met Tyr Phe Ile Lys
                85                  90                  95

Ser Thr Arg Glu Ser Leu Ile Ala Glu Glu Lys Met Ile Leu Thr Gly
            100                 105                 110

Asp Cys Cys Tyr Leu Ser Pro Leu Leu Arg Arg Ile Val Arg Phe Ile
        115                 120                 125

Gly Val Phe Ala Phe Gly Leu Phe Ala Thr Asp Ile Phe Val Asn Ala
    130                 135                 140

Gly Gln Val Val Thr Gly His Leu Thr Pro Tyr Phe Leu Thr Val Cys
145                 150                 155                 160

Gln Pro Asn Tyr Thr Ser Thr Asp Cys Arg Ala His His Gln Phe Ile
                165                 170                 175

Asn Asn Gly Asn Ile Cys Thr Gly Asp Leu Glu Val Ile Glu Lys Ala
            180                 185                 190

Arg Arg Ser Phe Pro Ser Lys His Ala Ala Leu Ser Ile Tyr Ser Ala
        195                 200                 205

Leu Tyr Ala Thr Met Tyr Ile Thr Ser Thr Ile Lys Thr Lys Ser Ser
    210                 215                 220

Arg Leu Ala Lys Pro Val Leu Cys Leu Gly Asp Leu Cys Thr Ala Phe
225                 230                 235                 240

Leu Thr Gly Leu Asn Arg Val Ser Glu Tyr Arg Asn His Cys Ser Asp
                245                 250                 255

Val Ile Ala Gly Phe Ile Leu Gly Thr Ala Val Ala Leu Phe Leu Gly
            260                 265                 270
```

```
Met Cys Val Val His Asn Phe Lys Gly Thr Gln Gly Ser Ala Ser Lys
        275                 280                 285

Pro Lys Pro Glu Asp Pro Arg Gly Val Pro Leu Met Ala Phe Pro Arg
    290                 295                 300

Ile Glu Ser Pro Leu Glu Thr Leu Ser Ala Gln Asn His Ser Ala Ser
305                 310                 315                 320

Met Thr Glu Val Thr
                325
```

<210> 12
<211> 343
<212> PRT
<213> Rattus norvegicus

<400> 12

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Met Ala Gly Gly Arg Pro His Leu Lys Arg Ser Phe Ser Ile Ile Pro
1               5                   10                  15

Cys Phe Val Phe Val Glu Ser Val Leu Leu Gly Ile Val Val Leu Leu
            20                  25                  30

Ala Tyr Arg Leu Glu Phe Thr Asp Thr Phe Pro Val His Thr Gln Gly
        35                  40                  45

Phe Phe Cys Tyr Asp Ser Ala Tyr Ala Lys Pro Tyr Pro Gly Pro Glu
    50                  55                  60

Ala Ala Ser Arg Ala Pro Pro Ala Leu Ile Tyr Ala Leu Val Thr Ala
65                  70                  75                  80

Gly Pro Thr Leu Thr Ile Leu Leu Gly Glu Leu Ala Arg Ala Phe Phe
                85                  90                  95

Pro Ala Pro Pro Ser Ser Ser Pro Val Ser Gly Glu Ser Thr Ile Val
            100                 105                 110

Ser Gly Ala Cys Cys Arg Phe Ser Pro Pro Leu Arg Arg Leu Val Arg
        115                 120                 125

Phe Leu Gly Val Tyr Ser Phe Gly Leu Phe Thr Thr Thr Ile Phe Ala
    130                 135                 140

Asn Ala Gly Gln Val Val Thr Gly Asn Pro Thr Pro His Phe Leu Ser
145                 150                 155                 160
```

```
Val Cys Arg Pro Asn Tyr Thr Ala Leu Gly Cys Pro Pro Pro Ser Pro
                165                 170                 175

Asp Arg Pro Gly Pro Asp Arg Phe Val Thr Asp Gln Ser Ala Cys Ala
            180                 185                 190

Gly Ser Pro Ser Leu Val Ala Ala Ala Arg Arg Ala Phe Pro Cys Lys
        195                 200                 205

Asp Ala Ala Leu Cys Ala Tyr Ala Val Thr Tyr Thr Ala Met Tyr Val
    210                 215                 220

Thr Leu Val Phe Arg Val Lys Gly Ser Arg Leu Val Lys Pro Ser Leu
225                 230                 235                 240

Cys Leu Ala Leu Leu Cys Pro Ala Phe Leu Val Gly Val Val Arg Val
                245                 250                 255

Ala Glu Tyr Arg Asn His Trp Ser Asp Val Leu Ala Gly Phe Leu Thr
            260                 265                 270

Gly Ala Ala Ile Ala Thr Phe Leu Val Thr Cys Val Val His Asn Phe
        275                 280                 285

Gln Ser Arg Pro His Ser Gly Arg Arg Leu Ser Pro Trp Glu Asp Leu
    290                 295                 300

Ser Gln Ala Pro Thr Met Asp Ser Pro Leu Glu Lys Asn Pro Arg Pro
305                 310                 315                 320

Ala Gly Arg Ile Arg His Arg His Gly Ser Pro His Pro Ser Arg Arg
                325                 330                 335

Thr Val Pro Ala Val Ala Thr
            340
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<210> 13
<211> 5083
<212> DNA
<213> Homo sapiens

<400> 13
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agcttggagg agggagctgg acgtcgtctc tcgccagaaa aacggggagc aggagccaga 120

ctaaaggagg aagaggactg gcccgctcag ggaatagctg ggttgctgca aaaaggggcg 180

gggagaaggc gggggcgctg catgcagcgc gctggctcca gcggtggccg cggggaatgt 240

gacatcagcg gcgccgggcg cttggggctg gaggaggcgg ctcgcctcag ctgcgctgtg 300

cacacctcgc ccgggggagg acgcagaccc gggcaggcgg cagggatgtc ggcgaaggag 360

aggccaaagg gcaaagtgat caaggacagc gtcaccctcc tgccctgctt ttatttcgtc 420

gagttgccta tattggcatc atcggtggtt agcctctatt tcctcgaact cacagatgtc 480

ttcaaacctg tgcactctgg atttagctgc tatgaccgga gtcttagcat gccgtacatt 540

gaaccaaccc aggaggcaat tccattcctc atgttgctta gcttggcttt tgctggacct 600

gcaattacga ttatggtagg agaaggaatt ctctactgtt gcctctccaa aagaagaaat 660

ggggtcggac tagagcccaa cattaatgct ggaggctgca acttcaattc cttcctcaga 720

cgagctgtca gattcgttgg tgttcatgta tttggattat gctctacagc tctcattaca 780

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gggctaacac ggataactca gtataagaac cacccagttg atgtctattg tggcttttta 1140

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ggcatcctca accgaaacca cagagatgct agctctctga caaatctcaa aagagcaaat 1380

gctgatgtgg aaatcattac tccacggagc cccatgggga aggagaacat ggttaccttc 1440

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caccatggtc ctggcaatca gtacctcaaa atccagcctg gcgctgtccc cggatgtaac 1740

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cgggccaagt ggttaaaagc tgctgaaaag actgtggcct gtaacagaag caacagccag 1920

ccccgaatca tgcaagtcat agccatgtcc aagcagcagg gtgtcctcca aagcagcccc 1980

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cttctggcaa tttccttctc agagagggga gtgggaataa aatgttgcct tccccacttc 4320

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cttctctagt cattgaagtt ttttttttctt tacataaata ttgatatatt ctttttctac 4560

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catataatga tagacactag aactcagacc tctgcatgta tatttgataa catgtctttt 4680

gtaaaacaaa aattacaaaa aaatttgttt acattccact ggtaccttaa tttaaaataa 4740

atcagactaa aaggtggtat ctcttcttag tgttctattt atcttatttg ctaatgggag 4800

cacttcttcc tttgttaggc tgtgctttac tgataaaacc aagtattgaa taaagagagt 4860

taattatctt tttaaagtaa ataaaattat gaaaatatat atagtatata taaagtcctg 4920

tgtttaaaaa aatgttatgc aatgttttcc aaactgataa agtttgtaaa gtgctataaa 4980

tgtattttgt taagtacaga taaaagctat tgtgtgagta tattgtgcta aaatcataga 5040

aataaagatt agatttcttc atcaaaaaaa aaaaaaaaaa aaa 5083

<210> 14
<211> 2356
<212> DNA
<213> Homo sapiens

<400> 14
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tgcttctact tcgtggagct gcccatagtg gcttcttcca tcgtatcctt gtacttcctg 180

gagctgaccg acctcttcaa gccggccaag gtgggcttcc agtgctatga ccgcactctc 240

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gccttcgcgg cccctgccgc ctcgatcatg gtggccgagg gcatgttgta ctgtctgcag 360

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